Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Addison's Disease Self Help Group (ADSHG)	Guideline	003	012	Suggest that throughout the entire guideline, it needs to be clearer as to what is done in primary care and what is done in secondary care.	Thank you for your comment. NICE guidance does not usually specify where care is provided as this is determined locally based on clinical need.
Addison's Disease Self Help Group (ADSHG)	Guideline	003	012	Would also like to see emphasis on the role of specialist nurses, patient advice lines and access to nursing units for those without local provision. At present the provision of emergency kits and education is poor, even with the advent of the steroid NPSA. Every susceptible individual needs appropriate care and education.	Thank you for your comment. The committee agree providing patients and carers with information and support is important and have made recommendations on how to access medical advice and care, and to signpost people to any support groups and charities available.
Addison's Disease Self Help Group (ADSHG)	Guideline	004	023	Suggest in addition to comment on education on timing of medication when travelling, the impact of temperature on medication dosing also noted. When travelling to countries (or during UK heat waves) where high ambient temperatures, potential need to increase mineralocorticoid dose and/or salt intake through food.	Thank you for your suggestion. More information on managing medication when travelling has been added to the committee discussion in Evidence review A Information and support.
Addison's Disease Self Help Group (ADSHG)	Guideline	005	001	More emphasis needed on system management, particularly the role of primary care. Commissioners would value advice regarding standards of care, and this guidance is an opportunity to set expectations re: access to phone advice, use of advice and guidance, links between primary and secondary care and secondary and tertiary care.	Thank you for your comment. NICE guidance does not usually specify where care is provided or how this is organised as this is determined locally based on clinical need. Not all people with Adrenal Insufficiency would require secondary care services and would receive care from primary care with support from secondary care where needed. The recommendations include how to seek clinical advice, providing management plans and advice to health providers in other settings, and information on any support groups and charities available.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					The committee agrees the aim if the recommendations is to provide guidance on what information and support should be provided to people with Adrenal Insufficiency.
Addison's Disease Self Help Group (ADSHG)	Guideline	006	003	Suggest starting the list of signs and symptoms with fatigue, which is a dominant and highly prevalent symptom and less severe than "lethargy" mentioned further down that list. Suggest combining signs and symptoms in this list according to effect (e.g. list salt craving and blood pressure in conjunction with hyponatraemia and hypokalaemia or list signs and symptoms in order of frequency of occurrence. Suggest differentiating chronic signs and symptoms and acute, urgent signs and symptoms. (Fatigue is prominently mentioned in Box 1 on page 23).	Thank you for your comment. The items have been listed in the order of most to least clinically distinguishing. It's a common symptom and not uniquely linked to Adrenal Insufficiency.
Addison's Disease Self Help Group (ADSHG)	Guideline	007	004	Add "Adrenoleukodystrophy and Adrenomyeloneuropathy" to the list of co-existing conditions. This is really important and needs adding please.	Thank you for your suggestion but Adrenoleukodystrophy and Adrenomyeloneuropathy are rare, and the committee wanted to highlight the common coexisting conditions. Some text has been added to the 'committee discussion of the evidence' section in Evidence review B to highlight these conditions.
Addison's Disease Self Help Group (ADSHG)	Guideline	007	004	Consider summarising signs and symptoms of autoimmune polyendocrinopathy syndrome type 2 into one point (including autoimmune thyroid disease, premature ovarian insufficiency, type 1 diabetes, and also add vitiligo to that list) as you have APS1 as a single point without detailing signs and symptoms (would	Thank you for your comment. Type 1 has been removed from autoimmune polyendocrinopathy syndrome to include both forms.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				add this, chronic mucocutaneous candidiasis, primary hypoparathyroidism etc.).	
Addison's Disease Self Help Group (ADSHG)	Guideline	007	017	When acute presentation is suspected by primary care patient is at risk of adrenal crisis so should be sent to A&E to receive hydrocortisone immediately. Acute presentation diagnostic steps can then be taken whilst the patient is an inpatient/ in hospital, removing potential harm from untreated adrenal crisis whilst waiting for referral. Should be noted hydrocortisone can do no harm, but not receiving treatment for time-critical adrenal crisis be fatal – to reassure primary care and prompt a time urgent response.	Thank you for your comment. A link to the emergency management of adrenal crisis has been added to this section.
Addison's Disease Self Help Group (ADSHG)	Guideline	007	017	Initial investigations – strongly suggest differentiating diagnostic steps for an acute presentation with suspected adrenal crisis, and chronic signs and symptoms that may or may not result from underlying AI.	Thank you for your comment. A link to the emergency management of adrenal crisis has been added to this section.
Addison's Disease Self Help Group (ADSHG)	Guideline	007	017	With acute presentation, highly useful to take serum cortisol paired with plasma ACTH at any time of the day – restricting serum cortisol to morning values is only relevant with chronic symptoms and signs – this is really important and needs changing.	Thank you for your comment. The committee do not think it is practical to pair these tests as cortisol may be carried out within a generalist setting but ACTH can't and there's no data to support this.
Addison's Disease Self Help Group (ADSHG)	Guideline	007	017	Initial investigations – mentioning morning serum cortisol is not sufficient – at least further diagnostic steps following referral to the endocrine specialist team should be outlined (as nicely done in recommendation 1.7 describing all steps across primary and secondary care),	Thank you for your comment. A cortisol test could be taken within a generalist setting, but further tests would usually be referred on to secondary care as outlined in table 1.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				including short synacthen test, assessment of mineralocorticoid reserve, differentiation of primary and secondary AI and, very importantly, the identification of the underlying cause of AI. It is paramount that this mentions that people with primary AI who do not have increased adrenal autoantibodies need testing for very long chain fatty acids (VLCFA) to rule out or identify co-existing adrenoleukodystrophy or adrenomyeloneuropathy.	The investigation of underlying causes of Adrenal Insufficiency is outside of the scope of this guideline. Some text has been added to the 'committee's discussion of the evidence' section in Evidence review B to highlight these conditions.
Addison's Disease Self Help Group (ADSHG)	Guideline	008	001	Table 1 Would like to see more clarity regarding who is responsible for starting treatment (eg primary care), when to admit and what standards should be in place for urgent/routine referrals. The current waiting times represent a clear risk and commissioners should set standards.	Thank you for your comment. NICE guidance does not usually specify where care is provided as this is determined locally based on clinical need. Not all people with Adrenal Insufficiency would require secondary care services and would receive care from primary care with support from secondary care where needed.
Addison's Disease Self Help Group (ADSHG)	Guideline	008	002	We are concerned this may lead to delay in diagnosis/ adrenal crisis due to lack of clarity between acute presentation and chronic signs and symptoms. Suggest a preamble to the entire section and differentiate between acute and chronic signs and symptoms.	Thank you for your comment. This has been clarified by adding a recommendation to direct the reader to the emergency management section if adrenal crisis is suspected.
Addison's Disease Self Help Group (ADSHG)	Guideline	008	007	Rec 1.2.7 – should start with "If people show no acute but chronic signs and symptoms potentially indicative of AI, then advise them to…"	Thank you for your comment. The committee has made a recommendation that if adrenal crisis is suspected in a person taking oral oestrogens a serum cortisol test may still be carried out,

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Testing for AI cannot be delayed by several weeks just because person is on oestrogen, if signs suggest acute Adrenal Insufficiency or people are significantly symptomatic. Timely diagnosis is key.	but this should be taken into account when interpreting the results. A recommendation has also been added to the beginning of the initial investigations for Adrenal Insufficiency section to direct the reader to the emergency management section if adrenal crisis is suspected.
Addison's Disease Self Help Group (ADSHG)	Guideline	008	007	To avoid misinterpretation you could also combine 1.27 with 1.2.8 to a single point – experience tells that people are hung up on subpoints on a guideline and do not necessarily take into account additional information if hidden in a different, even subsequent point.	Thank you for your comment. Because the recommendations apply to different populations and situations the committee thinks the recommendations should be separate. However, to avoid delays a recommendation has been added to the beginning of the initial investigations for Adrenal Insufficiency section to direct the reader to the emergency management section if adrenal crisis is suspected.
Addison's Disease Self Help Group (ADSHG)	Guideline	009	010	Table 2 For secondary/tertiary Adrenal Insufficiency, lower hydrocortisone dose of 10-20 mg is fine, not advisable to treat these patients with full primary AI hydrocortisone dose unless undetectable cortisol documented.	Thank you for your comment. Limited evidence was found comparing different doses of oral hydrocortisone for adults with secondary Adrenal Insufficiency, but the committee agreed it indicated total daily doses of hydrocortisone between 15-25 mg in divided doses were safe to use. This was also in line with their clinical expertise and reflected current practice.
Addison's Disease Self Help Group (ADSHG)	Guideline	009	010	Table 2 There is evidence that pump therapy should be under alternative glucocorticoid if patient remains severely unwell under presumed adequate treatment/no issues with compliance. Especially important for those who	Thank you for your comment. Continuous subcutaneous hydrocortisone pumps are not used in current practice in the NHS. Both studies identified in the clinical review used insulin pumps as the device for delivery. An insulin pump costs around £2,000 to £3,000 and should last 4

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				have undergone gastrointestinal surgery or have known gastric and absorption issues. Pump therapy has been successfully trialled in small groups, with high levels of acceptability, improved cognitive outcomes and decreased hospital admissions which would in the long term compensate for increased treatment costs. This does have to be used off licence however as hydrocortisone is not licenced subcutaneously. There is no evidence that subcutaneous pumps cause line infections – indeed these are the same lines that are used in T1DM and therefore I do not feel this is valid reasoning. References - Lovas references, Oksnes, 2014 - Khanna A, Khurana R, Kyriacou A, Davies R, Ray DW. Management of adrenocortical insufficiency with continuous subcutaneous hydrocortisone infusion: long-term experience in three patients. Endocrinol Diabetes Metab Case Rep. 2015;2015:150005. doi: 10.1530/EDM-15-0005. Epub 2015 May 1. PMID: 26124953; PMCID: PMC4482159. Russell G et al. Ultradian hydrocortisone replacement alters neuronal processing, emotional ambiguity, affect and fatigue in Adrenal Insufficiency: The PULSES trial. J	to 8 years according to the NHS website. In addition to the device cost, there would be the cost of associated consumables, the medicine and training for the person using the device and the cost of staff to support a service. The clinical evidence showed no clinically important benefit over oral hydrocortisone. In addition, device-related adverse events were reported. Overall, the evidence was of limited certainty and insufficient to support any recommendation.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Intern Med. 2024 Jan; 295(1): 51–67. doi: 10.1111/joim.13721. PMID: 37857352; PMCID: PMC10952319	
Addison's Disease Self Help Group (ADSHG)	Guideline	010	001	Table 2 Dexamethasone is not a desirable alternative to hydrocortisone or prednisolone in CAH treatment because of adverse metabolic side effects. Important, if it remains, to pair with warning that dexamethasone has no mineralocorticoid effect and switching hydrocortisone to dexamethasone can elicit an adrenal crisis in patients with mineralocorticoid deficiency if not on fludrocortisone.	Thank you for your comment. The table specifies Dexamethasone should be used only under specialist advice.
Addison's Disease Self Help Group (ADSHG)	Guideline	011	001	Table 3 It is important to add that mineralocorticoid dose should be increased if ambient temperatures are high, e.g. if travelling in countries with a hot climate (BTW, in Italy, patients routinely double their fludrocortisone during hot summers).	Thank you for your comment. Recommendations on Information and advice on taking medication when travelling is in the Information and support section of the guideline.
Addison's Disease Self Help Group (ADSHG)	Guideline	012	007	Rec 1.3.4 – There is evidence that pump therapy should be noted as an option but only for those where all routine daily replacement options (with no issues with compliance) have been tried, but the individual continues to have issues with absorption, undergone gastrointestinal surgery or has multiple admissions with adrenal crisis. Pump therapy has been successfully trialled in small groups, with high levels of acceptability, improved cognitive outcomes and decreased hospital	Thank you for your comment. Continuous subcutaneous hydrocortisone pumps are not routinely used in current practice in the NHS. Both studies identified in the clinical review used insulin pumps as the device for delivery. An insulin pump costs around £2,000 to £3,000 and should last 4 to 8 years according to the NHS website. In addition to the device cost, there would be the cost of associated consumables, the medicine and training for the person using the device and the cost of staff to

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				admissions which would in the long term compensate for increased treatment costs. This does have to be used off licence however as hydrocortisone is not licenced subcutaneously. There is no evidence that subcutaneous pumps cause line infections – indeed these are the same lines that are used in T1DM. References - Lovas references, Oksnes, 2014 - Khanna A, Khurana R, Kyriacou A, Davies R, Ray DW. Management of adrenocortical insufficiency with continuous subcutaneous hydrocortisone infusion: long-term experience in three patients. Endocrinol Diabetes Metab Case Rep. 2015;2015:150005. doi: 10.1530/EDM-15-0005. Epub 2015 May 1. PMID: 26124953; PMCID: PMC4482159. Russell G et al. Ultradian hydrocortisone replacement alters neuronal processing, emotional ambiguity, affect and fatigue in Adrenal Insufficiency: The PULSES trial. J Intern Med. 2024 Jan; 295(1): 51–67. doi: 10.1111/joim.13721. PMID: 37857352; PMCID: PMC10952319	support a service. The clinical evidence showed no clinically important benefit over oral hydrocortisone. In addition, device-related adverse events were reported. Overall, the evidence was of limited certainty and insufficient to support any recommendation.
Addison's Disease Self Help Group (ADSHG)	Guideline	013	002	Rec 1.3.7 – Clarify clinical responsibility for providing these prescriptions including needles/syringes. Secondary care can confirm to primary care contents of emergency kit based on these NICE guidelines, but	Thank you for your comment. NICE guidance does not usually specify how services are delivered, as this would be determined locally based on clinical need.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				should be clear primary care can prescribe all elements and should be on repeat prescriptions, as primary care are accessible to patients for renewals of emergency kit and this will help remove delay in patients having emergency kits. Cannot risk delay in patient getting an appointment with secondary care to replenish an emergency kit when used. This could lead to the patient going months without an emergency kit putting them at risk of adrenal crisis. Even waiting on a letter from secondary care in some Trusts can take many weeks. Primary care often cautious so needs to be clear they are able to include elements needed for emergency kits on patients' repeat prescriptions.	
Addison's Disease Self Help Group (ADSHG)	Guideline	013	009	Please add the following information - more than 1 vial should be prescribed for an emergency injection kit so individual has spare in case vial shatters and becomes unusable whilst person is in emergency situation. Multiple spares further needed so person can have multiple kits to access during emergency situations (such as at home, work and for travel), and for young people to allow for a kit at home and in school setting.)	Thank you for your comment. The committee did deliberate this when making the recommendations, but based on consensus agreed that one vial per kit was sufficient, but that 2 to 3 kits should be provided.
Addison's Disease Self Help Group (ADSHG)	Guideline	013	023	Despite best intentions, most patients do not have access to emergency kit training from an endocrine nurse. This leads to responsibility falling on primary care and relevant patient support groups. Should be noted	Thank you for your comment. The committee acknowledged the importance of training to ensure emergency management kits are used when required, and they made the following recommendation as a

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				that this training can be accessed from primary care and relevant patient support groups, until guaranteed and easily accessible support is available for all at secondary care. In review appointments secondary care can make sure emergency training has taken place and patients level of confidence on using emergency kit. Necessary to remove barriers to patients having an emergency kit and reassure primary care they are able to direct patients to training materials (such as print out step by step instructions and videos led by Professor John Wass provided by patient support group Addison's Disease Self Help Group.) Leaflets: https://www.addisonsdisease.org.uk/how-to-give-an-emergency-injection-leaflets-for-your-kit Videos: https://www.youtube.com/playlist?list=PL58H0D1LpwGpgCxw2-xhQ12gdfHEDpSgX	result: 'ensure people are trained on how to use the kit'. As this is not a service delivery guideline, the exact delivery of this training was not specified. The economic analysis assumed this may be delivered by a nurse, however the exact delivery method will need to be decided locally based on available resources and local clinical expertise. In the evidence review on 'Emergency management' there is discussion of different ways the training could be delivered both in the health economic analysis and in the committee's discussion of the evidence.
Addison's Disease Self Help Group (ADSHG)	Guideline	013	023	Recommend secondary care endocrine units arrange steroid education days/ emergency kit training which they can invite all patients (and those who support them) to as a 'refresher' on training for emergency kits, to help emphasise necessary education and access needed by patients to endocrine nurses. Not all hospitals currently do this, most support comes from patient support groups.	Thank you for your comment. A recommendation has been made to ensure that people are trained on how to use the kit. NICE guidance does not usually specify how services are delivered as this would be determined locally based on clinical need. available resources and clinical expertise.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Addison's Disease Self Help Group (ADSHG)	Guideline	017	001	Add a sentence on advising women with AI and pregnancy that hydrocortisone and also increased doses of hydrocortisone as in stress doses or injections will not damage the baby as hydrocortisone is broken down and inactivated in the placenta. This is critical to add as information to be given to a woman with AI planning pregnancy or being pregnant.	Thank you for your comment. Your suggested text has been added to the rationale and impact section.
Addison's Disease Self Help Group (ADSHG)	Guideline	018	013	Rec 1.5.1 – Remove "Consider". Sick-day dosing is required for psychological stress.	Thank you for your comment. The committee discussed the wide variation in factors and events that could lead to psychological stress, and the variation in what people find stressful and how they react making it difficult to determine whether a person would be at risk of adrenal crisis because of psychological stress. This, and the lack of evidence is described in the committee discussion and rationale sections of the guideline.
Addison's Disease Self Help Group (ADSHG)	Guideline	020	020	Suggest a preamble to the entire section for A&E and ambulance services with an emphasis on early assessment and the importance of not delaying treatment or a subheading to set out standards for A&E and ambulance services would also be welcome with an emphasis on early assessment and importance of not delaying treatment.	Thank you. More detail is provided in the rationale and committee discussion sections of the guideline. The committee have recommended that IV or IM hydrocortisone is given immediately, and a person should go to hospital immediately. Service delivery and standards would need to be determined locally and are outside of the scope of this guideline.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Addison's Disease Self Help Group (ADSHG)	Guideline	024	002	Suggest to be clearer throughout the entire guideline what is done in primary care and what is done in secondary care – lots of the listed monitoring items, e.g. "consider measuring plasma renin and adjust fludrocortisone dose" should certainly be done by the specialist endocrinologist and not in primary care – it will be useful to clearly divide this so that the GP know what they should do and what will happen in the specialist care setting.	Thank you for your comment. NICE guidance does not usually specify where care is provided, as this is determined locally based on clinical need. Not all people with Adrenal Insufficiency would require secondary care services and would receive care from primary care with support from secondary care where needed.
Addison's Disease Self Help Group (ADSHG)	Guideline	024	007	Rec 1.8.9 – Bone density scans for all people with Adrenal Insufficiency every 3 to 5 years adds cost to NHS. Those on physiological glucocorticoid replacement should not require regular scans, only when become symptomatic in which case referral to relevant speciality to monitor bone density should take place. Bone density scans only to be done depending on other risk factors, or when chronically overtreated with glucocorticoid replacement.	Thank you for your comment. The committee disagreed that bone scans are required only for people who are symptomatic but have amended the recommendation to at least once at 5 years post diagnosis. This reflects current practice.
Addison's Disease Self Help Group (ADSHG)	Guideline	028	021 – 022	Physiological replacement dose – agree with these numbers but feel that a caveat needs to be based upon a person's weight as a small slight female will have a very different physiological dose. Background - 15-20mg of hydrocortisone which equates to approximately 8mg/m2/day in a 70kg individual. Mass spectrometry and HPLC in combination with mathematical modelling it now transpires that cortisol production rate in normal subjects is approximately 5.7-	Thank you for your comment. The committee hope that clinicians will take this into account when prescribing – a clinician can choose to give less in particular circumstances

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				7.4 mg/m2/day, being significantly less than first calculated, equating to a dose closer to 10-15 mg/day. References - Kerrigan JR, Veldhuis JD, Leyo SA, Iranmanesh A, Rogol AD. Estimation of daily cortisol production and clearance rates in normal pubertal males by deconvolution analysis. The Journal of clinical endocrinology and metabolism. 1993;76(6):1505-10. Esteban NV, Loughlin T, Yergey AL, Zawadzki JK, Booth JD, Winterer JC, et al. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. The Journal of clinical endocrinology and metabolism. 1991;72(1):39-45	
Addison's Disease Self Help Group (ADSHG)	Guideline	029	012	Remove "sudden". Impact of chronic stress, such as caring for family member at end of life, or stressful periods at work, require increased dosing to get through that period of time. Should not be limited to "sudden" episodes only.	Thank you for your comment. No evidence was found for periods of chronic stress leading to adrenal crisis.
Addison's Disease Self Help Group (ADSHG)	Guideline	029	013	Further examples to "bereavement" need to be offered to help illustrate to those not familiar with condition. Suggest adding: final exams, significant life events such as wedding or divorce, stressful/turbulent times at work. These are the most frequent examples reported to us anecdotally which end up causing adrenal crisis as patient is unaware of need to up dose.	Thank you for your comment, further examples have been added.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Addison's Disease Self Help Group (ADSHG)	Guideline	029	024	Add "psychological stress" to help reinforce extra replacement medication is also needed for situations such as bereavement.	Thank you for your comment. Sick-day dosing applies mainly to physiological stress. There may be very short periods where sick day dosing is used for sudden, intense psychological and emotional stress, but practice varies.
Addison's Disease Self Help Group (ADSHG)	Guideline	037	001 – 005	There is evidence that pump therapy should be under alternative glucocorticoid if patient remains severely unwell under presumed adequate treatment/no issues with compliance. Especially important for those who have undergone gastrointestinal surgery or have known gastric and absorption issues. Pump therapy has been successfully trialled in small groups, with high levels of acceptability, improved cognitive outcomes and decreased hospital admissions which would in the long term compensate for increased treatment costs. This does have to be used off licence however as hydrocortisone is not licenced subcutaneously. There is no evidence that subcutaneous pumps cause line infections – indeed these are the same lines that are used in T1DM and therefore I do not feel this is valid reasoning. References - Lovas references, Oksnes, 2014 - Khanna A, Khurana R, Kyriacou A, Davies R, Ray DW. Management of adrenocortical	Thank you for your comment. Continuous subcutaneous hydrocortisone pumps are not routinely used in current practice in the NHS. Both studies identified in the clinical review used insulin pumps as the device for delivery. An insulin pump costs around £2,000 to £3,000 and should last 4 to 8 years according to the NHS website. In addition to the device cost, there would be the cost of associated consumables, the medicine and training for the person using the device and the cost of staff to support a service. The clinical evidence showed no clinically important benefit over oral hydrocortisone. In addition, device-related adverse events were reported. Overall, the evidence was of limited certainty and insufficient to support any recommendation.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
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Addison's Disease Self Help Group (ADSHG)	Rationale for drug treatment	001 – 002	001	There should be detail added on the relative mineralocorticoid activity of hydrocortisone (40 mg hydrocortisone = 100 ug fludrocortisone) and prednisolone/prednisone and it should be emphasised that dexamethasone lacks any mineralocorticoid activity.	Thank you, this section was provided for information and will not be revised.
Alex The Leukodystrophy Charity	Guideline	007	004	It is critical to add "Adrenoleukodystrophy (ALD) and Adrenomyeloneuropathy (AMN)" to the list of co-existing conditions.	Thank you for your suggestion but Adrenoleukodystrophy and Adrenomyeloneuropathy are rare, and the committee wanted to highlight the common coexisting conditions. Some text has been added to the 'committee discussion of the evidence' section in Evidence review B to highlight these conditions.
Alex The Leukodystrophy Charity	Guideline	007	017	In addition to initial investigations, details on the differential diagnosis, i.e. both the differentiation of primary vs. secondary Adrenal Insufficiency (AI) and the identification of underlying causes needs to be added.	Thank you for your comment. The focus of this guideline is on the acute and long-term management of Adrenal Insufficiency. The identification and management of underlying conditions and the differential diagnosis of

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Importantly, this should include the information that people with primary AI who are found not to have increased adrenal autoantibodies must have a blood test to look for increased very long chain fatty acids (VLCFA), typically seen in co-existing adrenoleukodystrophy or adrenomyeloneuropathy. A diagnosis of AI can precede the neurological symptoms of the disease (Zhu et al, Huffnagel et al, Dubey et al). 80% of males with ALD develop Adrenal Insufficiency. Unfortunately, adrenal symptoms are often aspecific/misdiagnosed, especially in young children, and the path to a diagnosis can therefore be a lengthy odyssey. Multiple potentially life-threatening episodes/admissions often occur before diagnosis. It is documented that adrenal crisis results in preventable deaths in ALD patients (see Ronghe et al, Dubey et al and case studies below), yet highly effective treatment can be instituted with timely diagnosis. Furthermore, failure to make rapid diagnosis of AI precludes timely diagnosis of ALD in such patients, who then often present with symptomatic cerebral ALD (CALD) too advanced for further therapy. We also know from published and anecdotal evidence that an AI diagnosis does not always lead to a timely ALD diagnosis. This precludes definitive treatment of CALD at early stage which in turn impacts long term	primary, secondary and tertiary Adrenal Insufficiency are outside the scope of this guideline. Some text has been added to the 'committee' discussion of the evidence' section in Evidence review B to highlight these conditions.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				neurological function and survival deleteriously (see Polgreen et al). Such delays have potentially grave implications for the patient and their family as illustrated by the patient case studies listed at the end of this section. Adrenal Insufficiency is not always easy to diagnose and sometimes there are rare causes of it that are difficult to identify and often take longer to diagnose, this includes ALD. The only comprehensive survey of this subject in the UK (Ronghe et al, reporting a decade's experience in South West England) found that diagnosis of Adrenal Insufficiency followed that of ALD in 50% of cases rather than preceding it. Alex TLC's experience and beneficiary reports further emphasise the difficulties of Adrenal Insufficiency diagnosis and relevant testing for ALD. Further evidence for submission: The Natural History of Adrenal Insufficiency in X-Linked Adrenoleukodystrophy: An International Collaboration Huffnagel et al https://pubmed.ncbi.nlm.nih.gov/30252065/ The Changing Face of Adrenoleukodystrophy Zhu et al https://academic.oup.com/edrv/article/41/4/577/5828725	

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Adrenal Insufficiency In Asymptomatic Adrenoleukodystrophy Patients Identified By Very Long-Chain Fatty Acid Screening Dubey et al https://pubmed.ncbi.nlm.nih.gov/15812458/ Importance of family history in patients with adrenoleukodystrophy Das et al https://academic.oup.com/qjmed/article/103/8/628/1522619 X-linked Adrenoleukodystrophy in a 20-Year-Old Male With an ABCD1 Gene Mutation: First Case From Pakistan Ghori et al https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8896247/ The importance of testing for adrenoleukodystrophy in males with idiopathic Addison's disease Ronghe et al https://adc.bmj.com/content/86/3/185 Early diagnosis of cerebral X-linked adrenoleukodystrophy in boys with Addison's disease improves survival and neurological outcomes	

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Polgreen et al https://pubmed.ncbi.nlm.nih.gov/21279382/ Adrenoleukodystrophy in the Differential Diagnosis of Boys Presenting with Primary Adrenal Insufficiency without Adrenal Antibodies Ryalls et al https://pubmed.ncbi.nlm.nih.gov/32394691/ Normal overall mortality rate in Addison's disease, but young patients are at risk of premature death Erichsen et al https://pubmed.ncbi.nlm.nih.gov/19011006/ Premature mortality in patients with Addison's disease: a population-based study Bergthorsdottir et al https://pubmed.ncbi.nlm.nih.gov/16968806/ Highly informative case studies from families represented by Alex TLC are as follows: 1. One family lost a young son, aged 7 years, in 2015 to an Addisonian crisis with ALD being diagnosed as the cause of his AI at post-mortem. From this her other son was also diagnosed and is now being treated for AI and monitored for CALD.	

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				2. A mother was alerted to a diagnosis of AI in their family through her maternal brother. Two of her sons were then diagnosed with AI. After researching causes of AI on the internet she asked her GP to test for ALD and was initially refused, being told it was too unlikely as a diagnosis to be worthwhile pursuing. After a long fight for testing ALD was eventually confirmed. The initial MRI scan in her eldest son showed signs of active CALD. The mother herself took these scans urgently to a specialist and her son was admitted for urgent bone marrow transplantation. He is now a healthy adult working in HR management for the NHS. Her other son also developed CALD, received a bone marrow transplant in childhood and is now at university. 3. One family received an AI diagnosis after an adrenal crisis in their younger son. The father worked as a biochemist and fortuitously a colleague alerted him to the various causes of Adrenal Insufficiency and the family pushed for further testing for ALD. The initial MRI scan showed early signs of ALD and he was immediately admitted for bone marrow transplantation. He is now studying at university.	

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				4. One family repeatedly took their son to the GP after bouts of illness symptomatic of AI. Despite noting his skin colour (it is common for Addison/AI patients to have bronzed skin) he remained undiagnosed. He was later diagnosed with CALD, heartbreakingly at too advanced a stage for treatment. AI was still not diagnosed at this stage but three days after his ALD diagnosis he was admitted to A&E with an adrenal crisis and then spent one week in ICU. During this period, he lost his sight and subsequently died of CALD. However, thanks to his diagnosis, his brother was diagnosed with ALD, monitored for AI (onset at 2 years old), had a successful bone marrow transplant aged 8 years, attended university and is now in work in his early 20s. 5. One family had a misdiagnosis of ACTH receptor defect instead of AI in their young son (age 5). Unfortunately, a correct Adrenal Insufficiency diagnosis was not received until he was 25, following a diagnosis of cerebral ALD, and he now has severe behavioural issues, and progressive mobility and cognitive issues. Had he been diagnosed correctly in childhood, he may have been able to receive a bone marrow transplant.	

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				6. Another family had a successful diagnosis of Adrenal Insufficiency in their young son, but ALD was not identified despite a lengthy and traumatic diagnostic journey when behavioural symptoms began in his early teenage years. Subsequently, he deteriorated and ended up in a care facility, where he died. ALD was identified at post-mortem. 7. One man was diagnosed in his early 20s with Adrenal Insufficiency after a lengthy diagnostic process. He then went on to develop progressive AMN symptoms over a number of years, although these symptoms failed to prompt an ALD diagnosis. This is just a sample of patient experience, demonstrating the far-reaching implications of undiagnosed AI as well as highlighting the benefits that an early diagnosis can bring.	
Association for Laboratory Medicine	Guideline	007	021	Section1.2: Initial Identification and Referral/Initial Investigations for Adrenal Insufficiency (Not Including people withdrawing form exogeneous glucocorticoids) We recommend the acknowledgement that is not always practical to draw blood between 8-9am for cortisol levels, thus, guidance for action limits on other times e.g., for cortisol received between 10-noon would be useful.	Thank you for your comment. The evidence found was all for early morning cortisol tests. No reliable evidence was found to support other time frames. Cortisol tests carried out later in the day would not be of any clinical use as levels may be too low and could lead to unnecessary referrals

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Association for Laboratory Medicine	Guideline	007	021	Section 1.2: Initial Identification and Referral/Initial Investigations for Adrenal Insufficiency (Not Including people withdrawing form exogeneous glucocorticoids) We recommend as cortisol levels is subject to an individual's circadian rhythm, and needs further consideration for night workers and that specifying the number of hours after waking may be more useful than an 8-9am cortisol level.	Thank you for your comment. The evidence found was all for early morning cortisol tests. No reliable evidence was found to support other time frames. Furthermore, no normal ranges have been identified in night workers and so specifying a number of hours after waking would not be of diagnostic utility. The circadian clock shifts 1 hour in 24 hours and so timings may depend on how many nights have been worked. For night workers the health care professional will need to avoid testing straight after a night shift or consider a different diagnostic test for example a short synacthen test or alternatively wait 3-4 days after a night shift.
Association for Laboratory Medicine	Guideline	007	021	Section 1.2: Initial Identification and Referral/Initial Investigations for Adrenal Insufficiency (Not Including people withdrawing form exogeneous glucocorticoids) We are concerned that the recommendation of 8-9am cortisol is not appropriate for all individuals e.g. night-workers.	Thank you for your comment. The evidence found was all for early morning cortisol tests. No reliable evidence was found to support other time frames. Cortisol tests carried out later in the day would not be of any clinical use as levels may be too low and could lead to unnecessary referrals. For night workers, the health care professional will need to avoid testing straight after a night shift or consider a different diagnostic test for example a short Synacthen test or alternatively wait 3-4 days after a night shift.
Association for Laboratory Medicine	Guideline	008	001	Section 1.2: Initial Identification and Referral/Initial Investigations for Adrenal Insufficiency (Not Including people withdrawing form exogeneous glucocorticoids) Table 1 does not provide details of the cortisol methodology/assay from which the tabulated actionary	Thank you for your comment. Providing details of cortisol assay methodology is beyond the scope of this guidelines. The reference ranges will depend on the type of assays used. Test results should be interpreted based on established local assays and corresponding cut-offs.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				serum cortisol levels are derived. We strongly recommend to inform that there is lack of standardisation between cortisol assays and to advise that an understanding of method-specific cut-offs should be used.	The following clarification can be found in the rationale and impact section and the 'committee discussion of the evidence' section in Evidence review D: *The committee discussed the difficulties in setting cut-off points, as these vary greatly depending on the assay used and only have clinical use if specific to a particular assay. However, the committee agreed that it would be useful for non-specialists to have some guidance on at what point to refer onwards (providing it is highlighted that the cut-offs are only for use with modern immunoassay assays and that local guidelines may need to be followed if alternative assays are used).*
Association for Laboratory Medicine	Guideline	008	001	Section 1.2: Initial Identification and Referral/Initial Investigations for Adrenal Insufficiency (Not Including people withdrawing form exogeneous glucocorticoids) We are concerned that serum cortisol cut-offs stated in table 1 would be used indiscriminately of the cortisol assay used.	Thank you for your comment. Providing details of cortisol assay methodology is beyond the scope of this guidelines. The reference ranges will depend on the type of assays used. Test results should be interpreted based on established local assays and corresponding cut-offs. The following clarification can be found in the 'committee discussion of the evidence' section in Evidence review D: *The committee discussed the difficulties in setting cut-off points, as these vary greatly depending on the assay*

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					used and only have clinical use if specific to a particular assay. However, the committee agreed that it would be useful for non-specialists to have some guidance on at what point to refer onwards (providing it is highlighted that the cut-offs are only for use with modern immunoassay assays and that local guidelines may need to be followed if alternative assays are used).
Association for Laboratory Medicine	Guideline	008	001	Section 1.2: I Initial Identification and Referral/Initial Investigations for Adrenal Insufficiency (Not Including people withdrawing form exogeneous glucocorticoids) We cannot state agreement with the serum cortisol cut-offs in table 1 because the methodology /cortisol assay source of these cut-offs is not referenced.	Thank you for your comment. Evidence review D includes the evidence underpinning these recommendations. Table 2 in evidence review D includes a description of the assays used in each of the included studies. It is beyond the scope this guideline to comment on specific assays to be used. In practice, the reference ranges will depend on the type of assays used. Test results should be interpreted based on established local assays and corresponding cut-offs.
Association for Laboratory Medicine	Guideline	008	001	Section 1.2 Initial Identification and Referral/Initial Investigations for Adrenal Insufficiency (Not Including people withdrawing form exogeneous glucocorticoids) We recommend to include information & advise on the measurement and interpretation of ACTH serum levels for distinguishing between primary, secondary & tertiary Adrenal Insufficiency.	Thank you for your comment. The committee does not think this is necessary because the recommendations have been amended to refer a person to endocrinology services if they have a serum cortisol level below 300 nmol/L where specialists would interpret test results. Differential diagnosis of primary, secondary, and tertiary Adrenal Insufficiency was not included in the scope of this guideline.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Association for Laboratory Medicine	Guideline	009	010 – 011	Section 1.3 : Routine Pharmacological management. Table 2. There is no guidance on how to distinguish secondary and tertiary Adrenal Insufficiency from primary Adrenal Insufficiency with regard to the measurement and interpretation of ACTH serum levels.	Thank you for your comment. Differential diagnosis of primary, secondary, and tertiary Adrenal Insufficiency was not included in the scope of this guideline.
Association for Laboratory Medicine	Guideline	009	010 – 011	Section 1.3 : Routine Pharmacological management Table 2. There is no basis that prednisolone should be given in multiple doses. We are concerned that multiple dosing would increase the risk of over replacement, especially as the AUC (or steroid exposure) of prednisolone from 2mg BD is far higher than 4mg OD.	Thank you for your comment. Prednisolone administered in 1-2 divided doses has been removed from the table. No evidence meeting the inclusion criteria was found for Prednisolone and therefore the committee made recommendations on the dosage based on consensus.
Association for Laboratory Medicine	Guideline	010	007 – 008	Section 1.3 : Routine Pharmacological management. Table 3. There is no guidance on how to distinguish secondary and tertiary Adrenal Insufficiency from primary Adrenal Insufficiency with regard to the measurement and interpretation of ACTH serum levels.	Thank you for your comment. Differential diagnosis of primary, secondary and tertiary Adrenal Insufficiency was not included in the scope of this guideline.
Association for Laboratory Medicine	Guideline	010	007 – 008	Section 1.3 : Routine Pharmacological management. Table 3. There is no basis that prednisolone should be given in multiple doses. We are concerned that multiple dosing would increase the risk of over replacement, especially as the AUC (or steroid exposure) of prednisolone from 2mg BD is far higher than 4mg OD.	Thank you for your comment. The committee agreed for people under 16 years the dose may be divided if preferred but because of levels being too low overnight, some paediatricians prefer to split the dose. Prednisolone has an elimination half-life of 3 hours and even with acknowledging its pharmacodynamic effect is potentially longer, the duration may be too short for suppressing morning 17OHP. The cumulative effect may be higher from 2mg BD to 4mg OD however this is at replacement dose levels and would only usually be for

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					a year or two until the young person moves to adult care.
Association for Laboratory Medicine	Guideline	012	001	Section 1.3 : Routine Pharmacological management. Table 4. There is no guidance on how to distinguish secondary and tertiary Adrenal Insufficiency from primary Adrenal Insufficiency with regard to the measurement and interpretation of ACTH serum levels.	Thank you for your comment. Differential diagnosis of primary, secondary, and tertiary Adrenal Insufficiency was not included in the scope of this guideline.
Association for Laboratory Medicine	Guideline	012	010	Section 1.3: Routine Pharmacological management. Subsection 1.3.5: Sodium chloride supplementation is only really recognised in infants and children. We are not aware of good evidence of its use in adults (with the exception of a very old paper before the discovery of cortisone acetate in the 50's). We are concerned that this suggestion may provoke the use of sodium chloride in patients who are undertreated with glucocorticoid and/or mineralocorticoid replacement. An individuals' requirements do change with age and should be assessed with day curves. Also there is the risk of missing another concurrent diagnosis that is causing the hyponatraemia. From our clinical experience as a metabolic consultant sodium chloride has not been required in treating 100-1000's of patients in our Adrenal Insufficiency patient clinics.	Thank you for your comment. The recommendation is for all people with Adrenal Insufficiency. There is no strong evidence but in the committee's experience adults who are physically active can require further supplementation with sodium chloride.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Association for Laboratory Medicine	Guideline	014	010	Section 1.4 Management during Physiological Stress -1.4.2: It is not clear how significant physiological stress was defined. The accepted practice is to double the glucocorticoid dose. We are concerned that there is an absence of evidence to suggest a minimum of hydrocortisone dose of 40mg and prednisolone dose of 10mg, this recommendation may lead to the risk of over treating individuals. It is our opinion that this guideline should recommend doubling of the does instead of the suggesting doubling or tripling of dose as suggested by the endocrine society guidelines.	Thank you for your comment. The evidence base is limited but there is minimal risk of overtreatment, and the committee agreed there was a danger of leaving too large a gap without treatment by doubling the dose as suggested. Significant physiological stress would include fever, vomiting or diarrhoea. The committee recommended an increase to at least 40 mg a day because if someone is on hydrocortisone 2-3 times a day doubling the dose may not give sufficient rise in cortisol to cover acute physiological stress over a 24-hour period. In addition, some people are on a low dose such as 5mg three times a day and again doubling does not give sufficient 24-hour cover. Therefore, the committee agreed that for hydrocortisone the recommendation is 10mg four times a day. Similarly for prednisolone, some people may be on 3mg daily and doubling the dose would not be sufficient, which is why the committee recommended 5mg twice daily. A key part of sick day rules advice is to reduce glucocorticoids when physiological stress is resolving so as to reduce the time to the shortest period of 'increased glucocorticoid dosing'. .
Association for Laboratory Medicine	Guideline	027	026	Section 1.9 Managing glucocorticoid withdrawal to prevent Adrenal Insufficiency -1.9.8: The threshold for referring patient on weaning regimens based on morning cortisol is recommended as <300 nmol/L. We are concerned that this threshold	Thank you for your comment. The committee have reviewed and amended the recommendations to serum cortisol test results between 150-300 nmol/L to repeat the test and if the level remains the same seek advice from endocrinology

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				cortisol level is very high and that this recommendation will lead to an excess of referrals. We acknowledge that there a lack of evidence, but Pofi et al 2018 is probably the best evidence available. This paper has indicated that a random cortisol of >200 nmol/L is associated with a 100% recovery of axis at 4 years. The cut off value from the guidelines is far too high.	services. If the result is below 150 nmol/L glucocorticoids should be restarted and the person referred to endocrinology specialists.
Association for Laboratory Medicine	Guideline	028	018	Section 1.9 Managing glucocorticoid withdrawal to prevent Adrenal Insufficiency -1.9.8: Physiological equivalent dose section: We agree that 3mg is the physiological replacement dose for prednislone, however the issue is that this dose not correlate with the suggested doses in Table 2 and Table 3,	Thank you for your comment. The committee are aware that 3 mg may not enough for some people particularly if overweight therefore ranges are included to cover all eventualities. The dose ranges and an explanation that the dose may vary has been added to the terms used section of the guideline.
BNF Publications	Guideline	009	010	1.3.2 Table 2- We are seeking clarification on the adult fludrocortisone dose statement. Other fludrocortisone recommendations in the guideline include an initial dose, with advice to adjust as needed. Should these recommendations also be applied to the adult dose recommendation?	Thank you for your comment. The table has been amended to include 'initially' 50 micrograms and adjusted according to response up to 300 micrograms for adult doses.
BNF Publications	Guideline	009	010	1.3.2 Table 2- We have noted a difference in frequency of hydrocortisone dosing in secondary and tertiary Adrenal Insufficiency compared with primary. Is there a rationale for this difference?	Thank you for your comment. It is different because some people with primary Adrenal Insufficiency and T1D for example can have issues overnight with hypos and tend to have no cortisol whereas secondary and tertiary may have residual ACTH and so cortisol production and don't have the same issues generally, but clinical

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					judgement should still be used. The consensus among the committee was that a 4th dose is needed.
BNF Publications	Guideline	010	007	1.3.2 Table 3- We are seeking clarification on the paediatric fludrocortisone dose range. Is the intention for an initial dose to be 50micrograms, which can then be adjusted up to 300micrograms daily according to response (as per current BNFC recommendation)? Or is the initial dose anywhere between 50-300micrograms?	Thank you for your comment. The dose is initially 50 micrograms and adjusted according to response up to 300 micrograms. This clarification has been added to the table 2 and 3.
BNF Publications	Guideline	012	001	1.3.2 Table 4- We are concerned that the terminology 'in babies under 1 year' is not specific enough – does it includes children from birth e.g. neonates <1 month of age?	Thank you for your comment. Yes, it includes all babies under 1 year.
BNF Publications	Guideline	012	001	1.3.2 Table 4- We are seeking clarification on the fludrocortisone dose range. Is the intention for an initial dose to be 50micrograms, which can then be adjusted up to 200micrograms daily according to response (as per current BNFC recommendation)? Or is the initial dose anywhere between 50-200micrograms?	The dose is initially 50 micrograms and adjusted according to response up to 200 micrograms. This has been clarified within the table.
BNF Publications	Guideline	014	010	We are concerned that this recommendation differs from advice in the 2020 guidance from the RCP which recommends doubling the usual daily glucocorticoid use for moderate illness (see RCP guidance p375 sick day rules 1 https://www.rcpjournals.org/content/clinmedicine/20/4/37	Thank you for your comment. The committee agreed that doubling the dose is not enough for periods of intercurrent illness such as fever or vomiting. The committee acknowledges that the recommendations differ. The RCP guidance was written prior to the COVID pandemic. The committee noted that during the pandemic there was an increased incidence of adrenal

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				1.full.pdf). This could lead to uncertainty/confusion in practice.	crisis, and it was clear that doubling was not sufficient in all cases (such as when people were on lower maintenance doses of glucocorticoids). Therefore, the consensus from the committee was to recommend 10mg four times daily of hydrocortisone (40mg over 24 hours) or 5mg twice daily of prednisolone (10mg over 24 hours).
BNF Publications	Guideline	015	006	We are concerned that this recommendation differs from advice in the 2020 guidance from the RCP which recommends that for severe illness, either hydrocortisone 200mg IV infusion over 24 hours, or 100mg IM followed by 50mg IM/IV every 6 hours - there is no initial 100mg IM stat dose specified in the draft NICE guidance. (See RCP guidance p376 sick day rule 2 https://www.rcpjournals.org/content/clinmedicine/20/4/371.full.pdf). This could lead to uncertainty/confusion in practice.	Thank you for your comment. This recommendation has been amended to clarify during periods of physiological stress 100mg IM or IV hydrocortisone is given and if still severely unwell 200mg IV hydrocortisone or 50mg IM or IV hydrocortisone is administered.
BNF Publications	Guideline	020	022	We are concerned that this recommendation is not specific. To more clearly reflect the Emergency Steroid Card, consider specifying a dose of 100mg hydrocortisone, or consider a link directly to the Emergency Steroid Card in this place in the text.	Thank you. Where the dosages are the same as those in the BNF they have not been replicated within the guideline recommendations. The reader should refer to the BNF for further information.
BNF Publications	Question	1		Question 1- We forsee that the extent of consensus-based dose statements may be a challenge to implement. Acknowledgement of off-licence use and	Thank you for your response. Off-label usage of fludrocortisone in people aged 16 and over has been highlighted within the recommendations.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				aligning with dosing in other current guidance may help users overcome some of these challenges.	Cross reference has been made to the BNF for dosing in specific populations.
BNF Publications	Question	4		Question 4- We acknowledge that dosing in this draft NICE guideline align with current practice and are therefore generally happy to support the guidelines. An off-label use statement is helpful where information differs from the product licensing. Differences in adult dosing recommendations in this draft NICE guidance compared with those in other recent adult guidance from 2020 (https://www.rcpjournals.org/content/clinmedicine/20/4/371.full.pdf) are difficult for us to reconcile within the BNF, and can lead to uncertainty/confusion in practice.	Thank you for your response. The committee acknowledge that the recommendations differ. The RCP guidance was written prior to the COVID pandemic. The committee noted that during the pandemic there was an increased incidence of adrenal crisis, and it was clear that doubling was not sufficient in all cases (such as when people were on lower maintenance doses of glucocorticoids). Off-label usage of fludrocortisone in people aged 16 and over has been highlighted within the recommendations. Cross reference has been made to the BNF for dosing in specific populations.
BNF Publications	Question	5		Question 5- We agree with this approach. It is helpful as it means there is no divergence in practice due to slight differences in the way information is presented between sources.	Thank you for your response.
BNF Publications	Question	6		Question 6- We agree with inclusion of this information and acknowledge the need to provide generalised guidance for non-endocrine specialist clinicians.	Thank you for your response.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	General	General	We appreciate that this is written with other practioners in mind rather than specialist endocrine teams. However, in view that monitoring is discussed which is managed by the specialist endocrine teams, should this document also include some discussion of identifying the underlying cause of the Adrenal Insufficiency, even if	Thank you for your comment. The scope of the guideline covers people with Adrenal Insufficiency and does not focus on underlying causes.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				it is simply to say that that the underlying cause for Adrenal Insufficiency which will have bearing on management and prognosis would be further investigated by the specialist endocrine teams. Given that this is also a document for patients and their families it is important for them to understand that trying to identify the underlying cause has bearing on their management and prognosis.	
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	004	010	Change to "(Plus mineralocorticoids *where required* for primary Adrenal Insufficiency) as not all forms of PAI result in mineralocorticoid deficiency	Thank you for your suggestion. Prescribing treatment would be made by the clinician based on the needs of the individual patient. The committee think the wording is clear.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	006	003	It is difficult to assess AI at the best of times as the symptoms are so vague, but a child and especially a baby/neonate or older child with learning difficulties will not be able to tell you any symptoms	Thank you for your comment. For babies or children with learning difficulties family members or carers would need to provide additional information to assist the clinician in identifying Adrenal Insufficiency.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	007	008	"autoimmune polyendocrinopathy syndromes" as PAI can be seen in both types 1 and 2	Thank you for your comment. This has been amended and type 1 has been removed to make clear both forms are included.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	007	021	Add "consider taking a baseline ACTH," this would also be informative paired with the cortisol result	Thank you for your comment. The committee do not think it is practical to pair these tests as cortisol may be carried out within a generalist setting but ACTH can't and there's no data to support this.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	008	001	Newborns and infants do not have a diurnal rhythm for several months and cortisol levels are much harder to interpret. It may be better to say that this table is not relevant for infants and newborns and that the results should be discussed with paediatric endocrinology in the context of the clinical situation	Thank you for your comment. A separate column has been made for children and young people under 16 years. A separate recommendation has been added for patients under the age of 1 cortisol can be measured at any time of day and results should be discussed with a specialist.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	008	001	Table 1 if you end up repeating the morning cortisols on a few occasions, it may have been easier to do a synacthen test, especially in the young, where venepuncture or access may be challenging	Thank you for your comment. The committee removed the option for short Synacthen tests as these would typically be carried out within endocrinology services and require referral, whereas serum cortisol tests can be carried out within primary care.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	008	001	Cortisol <150 nmol/L : "For children and young people less than 16 years discuss and refer to endocrinology urgently for further investigations and glucocorticoid replacement as required." We would not expect primary care/ other practitioners to start glucocorticoid replacement in children independently outside the acute setting.	Thank you for your comment. A separate column has been made for children and young people under 16 years that states if cortisol is below 150 nmol/L the patient should be referred to paediatric services.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	008	001	Table 1. ? separate action column for <16s withdrawing from steroids 150-200 – book *SST 201-300 if over 2 years repeat EMC within a week – if still low then start sick days and refer to endocrinology 201-300 under 2 years or multiple co-morbidities – *SST.	Thank you for your comment. A separate column has been made for children and young people under 16 years that states for cortisol under 300 nmol/L seek advice or refer to paediatric or paediatric endocrinology.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				* If SST will be delayed by more than a few days to start mainenance hydrocortisone, advise on sick day dosing, and omit for 12 hours prior to booked SST >300 Adrenal Insufficiency unlikely - ask parents/ carers to remain vigilant and report any symptoms If fails SST discuss urgently with endocrine team for further management.	
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	008	005	For newborns a random cortisol(s) may be the only option as newborns and infants do not have a diurnal rhythm for several months so any cortisol measurement will be random.	Thank you for your comment. The committee has made a recommendation that cortisol can be measured at any time of day for people under the age of 1.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	008	007	Can it be clarified if taking oral oestrogen includes the oral contraceptive pill (We presume it does).	Thank you for your comment. Oral oestrogen does include the contraceptive pill, and this is discussed within the committee discussion section of evidence review D.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	009	003	Change to "offer glucocorticoids and, where required, mineralocorticoids for people with primary Adrenal Insufficiency"	Thank you for your comment. The recommendation has been amended as suggested.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	012	001	At times infants with CAH may need hydrocortisone doses of over 15mg/m2?	Thank you for your comment. The recommendations are given as guidance. Dosages over 15mg/m2 are rarely used but may be required on occasion. Individual treatment decisions would need to be made by the clinician in partnership with the patient and/or carers.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	012	010	Sodium supplementation is commonly required in infants with primary Adrenal Insufficiency – discuss with endocrinology.	Thank you for your comment. The committee recognise sodium supplementation may be required and have recommended seeking specialist endocrinology advice to consider sodium chloride supplementation.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	012	011	Hydrocortisone sodium succinate 100 mg powder and 5- or 10-ml water for injection (1 vial). Can it be clarified that only 1ml would be required for reconstitution for the purposes of the IM injection?	Thank you for your comment. This has been clarified in the wording of the recommendation.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	013	004	For younger patients esp with multi-morbidity, an emergency kit should also be issued. For example children undergoing cancer treatment or young people with DMD with multiple morbidities, who regularly undergo treatment with IV bisphosphonates where symptomatic AI including severe complications like HDU/ICU admissions have been known. Emergency kits should not be provided following adrenal crisis, for sure adrenal crisis may be less common but usually with catastrophic outcomes.	Thank you for your comment. The committee agrees and has changed the recommendation to considering an emergency kit for: - All people with tertiary Adrenal Insufficiency who have a history of adrenal crisis. - People under 16 years who are being treated for tertiary Adrenal Insufficiency (with or without a history of adrenal crisis).
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	013	016	Include "these instructions should include how to prepare and give the required emergency dose of hydrocortisone for children and young people, which may only require administration of part of the vial	Thank you for your comment. Instructions on administration of individual products are provided by the BNF or SPC. The information and support recommendations also provide advice on the administration of glucocorticoid in an emergency situation.
British Society of Paediatric	Guideline	018	020	Psychological stress: For babies, children and young people up to 16 years….. can this be changed to	Thank you. This has been amended as suggested.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Endocrinology and Diabetes (BSPED)				'consider sick day dosing for 1 to 2 doses (or longer if indicated)' (rather than 1 to 2 days) and follow section 5.	
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	020	001	Hyperpigmentation is not present in those with secondary or tertiary AI- need to make a note that hyperpigmentation is also difficult to be clear in non white Caucasian individuals Hyponatraemia and hyperkalaemia also generally not present in those with secondary or tertiary AI. Also expect that even in PAI less likely to see sodium and potassium abnormalities when already on replacement treatment even if presenting with adrenal crisis.	Thank you for your comment. Clarification in the recommendations that hyperpigmentation is only seen in primary Adrenal Insufficiency have been made. Additions to the recommendation and the rationale and impact section have been made that this feature may not be easily recognised in people with black or brown skin and that clinicians should inspect buccal mucosa, surgical scars and ask the person if they have noticed any changes to their skin (see Committee discussion of the evidence (section 1.1.9.3 evidence review B). The committee agreed to remove hyperkalaemia from the list as this is uncommon. However, sodium disturbances are seen in secondary and tertiary Adrenal Insufficiency. The other features listed are appropriate.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	022	004	Children and young people under 16 years should be offered a face to face review at least 6 monthly to measure their height and weight and adjust glucocorticoid doses. Annually is too infrequent for this. Or Children and young people should have height and weight updated and reviewed for dose adjustment at	Thank you. The committee agreed that an appointment at least every 6 months and an annual face-to-face appointment, as a minimum, to measure height and weight, was appropriate. Additional appointments could be arranged if needed.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				least 6 monthly, and a face to face review at least every 12 months.	
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	023	017	Box 1 - Consider adding final sentence on under replacement. "In children and young people with congenital adrenal hyperplasia also consider under replacement if there is growth acceleration and early puberty"	Thank you for your comment. This has been amended to 'abnormal growth rate and timing of puberty' which applies to all children and young people with Adrenal Insufficiency.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	024	001	Box 2 - Add in Faltering growth in children	Thank you for your comment. This has been amended to 'abnormal growth rate and timing of puberty'.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	025	004	Add in " check their supply of emergency hydrocortisone injection is in date"	Thank you for your comment. Guidance on emergency management kits is provided in the guideline including checking the expiry date of hydrocortisone.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	025	007	Add in" and blood pressure"	Thank you for your comment. The list is not meant to be exhaustive, and it is not possible to cover every check that could be made. The committee have focused on the priority checks and monitoring.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	025	009	Check they are carrying/ wearing a medical alert card/ bracelet or necklace)from age 8 years or when able to go out for any period without a parent)	Thank you for your comment. Obtaining and using medical alerts and reviewing the changing needs of children as they grow up is included in the information and support section of the guideline.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	025	012	Bone density only required if concerns about bone health and not routinely needed once stopped growing	Thank you for your comment. The committee disagreed that bone scans are required only if there are concerns about bone health but have

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					amended the recommendation to at least once at 5 years post-diagnosis. This reflects current practice.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	027	005	Changing to HC: Often diff to get doses in younger children to physiological dosing with Pred, so consider changing to HC in younger children	Thank you for your comment. The recommendation has been clarified to indicate that changing from prednisolone to hydrocortisone may be considered in children.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	027	007	Add in "it is the responsibility of the clinician prescribing steroids to" tell people who are tapering ……..	Thank you for your comment. The committee thinks the wording is clear, the clinical team should advise the patient.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	027	013	How to suspect AI, This is not appropriate for younger children. Caveat needs to be put in. There are only retrospective studies that report low symptom frequency in children with AI post withdrawal (so these would have been excluded from the evidence base anyway, despite the reported frequency of 42% having AI after steroid withdrawal!) Those who are < 5 years old and / or have global delay / multiple co morbidities and / or safeguarding concern/ parenting concerns would have the greatest risk of subtle symptoms, where present, being missed	Thank you for your comment. The committee added to the discussion that in young people who are unable to communicate how they are feeling, clinicians and carers need to be vigilant in monitoring for signs of Adrenal Insufficiency. The committee recognises that the signs and symptoms can be subtle and easily missed. This information has been included in the summary of the committee's discussion in review B.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	027	017	All who discontinue long term oral steroids should have at least a morning cortisol, for example those who have been on > 12 months of oral steroids. In paediatrics, we often are faced with young individuals who have been treated with oral daily steroids for > 5 years. Also some may have "shorter" duration of steroids but have had	Thank you for your comment. The committee has added a recommendation for people under 16 to consider a cortisol test following tapering, even without symptoms or signs of Adrenal Insufficiency.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				multiple modality of steroid exposure. Waiting for symptoms is not appropriate- as discussed symptoms are not easy to ascertain in children; also overlap with some primary disease symptoms.	
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	027	017	Should also consider a morning cortisol for those who are < 5 years old and / or have global delay / multiple co morbidities and / or safeguarding concern/ parenting concerns would have the greatest risk of subtle symptoms, where present, being missed who have had 3 months or more of supraphysiological doses.	Thank you for your comment. The committee have added to the discussion that in young people not able to communicate how they are feeling clinicians and carers need to be vigilant in monitoring for signs of Adrenal Insufficiency as the signs and symptoms can be subtle and easily missed. This has been described in the committee discussion in review B. The committee have also added a recommendation for people under 16 to consider a cortisol test following tapering even without symptoms or signs of Adrenal Insufficiency.
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	027	026	I think the investigation pathway should follow the general investigation pathway. Here it says that when cortisol < 300 nmol/L to restart steroids.	Thank you for your comment. The serum cortisol table has been added to this section and amended to restart glucocorticoid if serum cortisol is below 150nmol/L and refer to endocrinology specialists
British Society of Paediatric Endocrinology and Diabetes (BSPED)	Guideline	028	009	If the result is below 300nmol/L consider restarting glucocorticoids and refer the person to endocrinology. In borderline values could this recommendation be softened and also add in ' or consider providing glucocorticoids for sick days and refer to endocrinology'?	Thank you for your comment. The committee have reviewed and amended the recommendations to a serum cortisol test result below 150 nmol/L glucocorticoids should be restarted, and the person referred to endocrinology specialists.
Diurnal Ltd	Evidence Review A	General	General	The literature search seems to have missed the following references which we believe relevant to the question:	Thank you for your comment. We have reviewed the references you have provided: Simpson et al., Journal of Genetic Counseling. https://doi.org/10.1007/s10897-018-0278-9

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Simpson et al., Journal of Genetic Counseling. https://doi.org/10.1007/s10897-018-0278-9 *Adrenal Insufficiency in Young Children: a Mixed Methods Study of Parents' Experiences* and Watson et al., International Journal of Pharmaceutics 545 (2018) 57–63 https://doi.org/10.1016/j.ijpharm.2018.04.054 These studies highlight the challenges for caregivers in preparing low hydrocortisone doses for their children from standard tablets.	This paper has been added to the review. Watson et al., International Journal of Pharmaceutics 545 (2018) 57–63 https://doi.org/10.1016/j.ijpharm.2018.04.054 This paper reports survey results. Surveys were excluded in accordance with the protocol for this review.
Diurnal Ltd	Evidence review F	General	General	We are concerned that terminology used to describe Plenadren (hydrocortisone modified-release tablets, authorised for treatment of AI in adults) and Efmody (hydrocortisone modified-release hard capsules, authorised for treatment of CAH in adults and children aged 12 and over) are confusing and do not allow the reader to distinguish between the products (e.g. including dual-release, modified release terminology). We note that Efmody is incorrectly referred to as tablets in the costing tables which confuses the issue further. Given that these formulations differ (e.g. posology once-daily vs twice daily) we are concerned that this could present a patient safety issue.	Thank you for your comment. The costing tables have been edited for Efmody. 'Dual-release' has been changed to 'modified-release' throughout the review except in when describing the studies in the summary of evidence tables. 'Dual' in brackets has been included next to modified release in the summary of studies table (table 2) to indicate they are the same. In the guideline it has now been clarified if the recommendations refer to tablets or capsules to distinguish between the two modified release hydrocortisone medicines.
Diurnal Ltd	Evidence Review F	006	035	Table 1 In this evidence review, androgen normalisation is used as a measure for effectiveness of therapy in CAH. Current treatment guidelines acknowledge that	Thank you for your comment. The committee agree that suppression of 17-OHP leads to overtreatment. No comment on management of CAH in this guideline has been made as it's outside scope.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				androgen normalisation is not achievable without using supraphysiological steroid dosing and so is not advisable with current therapies. This outcome should be considered only when current glucocorticoid therapy is able to be combined with other treatment modalities in the future.	The committee commented in recommendations only to use higher than replacement doses on specialist advice in CAH to take into account concerns of over replacement.
Diurnal Ltd	Evidence review F	007	001	While we understand methodologically why the Alkindi (hydrocortisone modified release hard capsules) single-arm Phase 3 study and Phase 4 extension [Neumann U, Braune K, Whitaker MJ, Wiegand S, Krude H, Porter J, Digweed D, Voet B, Ross RJM, Blankenstein O. A Prospective Study of Children Aged 0-8 Years with CAH and Adrenal Insufficiency Treated with Hydrocortisone Granules. J Clin Endocrinol Metab. 2021 Mar 8;106(3):e1433-e1440. doi: 10.1210/clinem/dgaa626. PMID: 32888021; PMCID: PMC7947757.] do not meet criteria for evidence review, and so are excluded from this document, we believe that in the absence of other evidence they should be referred to. The EMA and MHRA agreed that these studies were appropriate for the evaluation of this medicine, given that the variability of any individually prepared hydrocortisone would make it an unsuitable comparator. It is disappointing that a registrational study is not considered here whereas non-universal clinical practice use of off-label dose manipulation which is not evidence based is included (Table 8 and 16).	Thank you for your comment. The different formulations in the unit cost tables for children was illustrative to allow the committee to consider different costs in the absence of health economic evidence. These were based on the different approaches taken in current practice according to the committee. There was no evidence specifically comparing different formulations in children (alkindi granules versus crushing and dispersing or pill splitting). As stated in the committee discussion of the evidence the committee did not specify which approach or formulation to take in the recommendation due to the lack of comparative evidence. In conclusion, no recommendation was made advising people to crush tablets nor was a recommendation made stating this should not be done.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We would question whether this provides equity for parents and children in terms of access to evidence-based, dose-appropriate, high-quality treatments.	
Diurnal Ltd	Evidence Review F	008	010	1.1.4.1. Included studies It is surprising that Gagliardi et al 2014 has been excluded on the basis of comparator- the comparator is oral hydrocortisone, and although Australia has a preparation not available in the UK, it has been considered therapeutically equivalent to Alkindi by the TGA. Excluding this study removes one of the only blinded studies in the area.	Thank you for your comment. Gagliardi 2014 has been added to the review. The study could not be meta-analysed with any other studies due to the differences in comparators and outcomes. The committee agreed that the study did not show any clinically important difference in quality of life as measured by the Fatigue Scale and GHQ-28 for the use of continuous subcutaneous hydrocortisone infusion compared to oral hydrocortisone. Therefore, it did not change their decision and it did not lead to any changes in recommendations.
Diurnal Ltd	Evidence review F	008	010 – 011	1.1.4.1. Included studies Plenadren appears to be being referred to both as modified release hydrocortisone and dual release hydrocortisone- this is confusing for the reader. This could make it appear to the reader that the studies relate to different products, when this is not the case.	Thank you for your comment. 'Dual-release' has been changed to 'modified-release' throughout the review except in when describing the studies in the summary of evidence tables. 'Dual' has been added in brackets next to modified release in the summary of studies table (table 2) to indicate they are the same. In the guideline it has now been clarified if the recommendations refer to tablets or capsules to distinguish between the two modified release hydrocortisone medicines.
Diurnal Ltd	Evidence Review F	014	009	Table 5 1.1.6. Summary of the effectiveness evidence	Thank you for your comment. 5% is correct. It is the risk with the control (hydrocortisone TID).

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				There seems to be a misprint here "The mean change in HbA1c% from baseline was 5.0 %" should read "The mean change in HbA1c% from baseline was 0.1%"	
Diurnal Ltd	Evidence Review F	028	002	Table 13: Modified-release hydrocortisone compared to standard glucocorticoid in adults with congenital adrenal hyperplasia Attrition bias for this study (Merke et al., *J Clin Endocrinol Metab. . 2021 Apr 23;106(5):e2063-e2077*) is considered very high but attrition rate was 13.9%. NICE guidance suggests 40% is very high attrition bias.	Thank you for your comment. This was an error in the footnotes. The evidence from the study was not downgraded because of attrition bias but due to 'deviations from the intended interventions' as assessed using the Cochrane risk of bias tool 2.0. The footnote has been corrected.
Diurnal Ltd	Evidence Review F	033		Table 16 Crushing and dissolving hydrocortisone is mentioned with no reference to the inaccuracy of such a method- see *Watson C, Webb EA, Kerr S, Davies JH, Stirling H, Batchelor H. How close is the dose? Manipulation of 10 mg hydrocortisone tablets to provide appropriate doses to children. Int J Pharm. 2018 Jul 10;545(1-2):57-63. doi: 10.1016/j.ijpharm.2018.04.054. Epub 2018 Apr 26. PMID: 29705101.* Given Crushing and dissolving hydrocortisone are being recommended, we suggest that the guideline should include an evidence based method to accurately produce small doses of hydrocortisone (eg. 0.5-1mg) from tablets in the domestic environment.	Thank you for your comment. the different formulations in the unit cost table for children was illustrative to allow the committee to consider different costs in the absence of health economic evidence. These were based on the different approaches taken in current practice according to the committee. There was no evidence specifically comparing different formulations in children (alkindi granules versus crushing and dispersing or pill splitting). The reference you provide does not meet the protocol of this review question. As stated in the committee discussion of the evidence the committee did not specify which approach to take in the recommendation due to the lack of comparative evidence. Therefore, no recommendation was made advising people to crush tablets, nor was a recommendation made stating this should not be done.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Diurnal Ltd	Evidence review F	033 - 034		Table 16 and p34 lines 1-15 - Table 16 presents the costs of Alkindi and immediate release hydrocortisone (HC), and p34 lines 1-15 outline how a HC dose might be prepared for neonates and young children from standard hydrocortisone tablets. However, no mention is made that standard HC tablets available in UK are not authorised for use in this fashion, and so delivered doses are not subject to the degree of regulation and quality control mandated for a licensed drug manufacturer. Furthermore, when asked, manufacturers do not have data for or recommend such manipulation of their products. A neonate may require a 3mg total daily dose administered over 3 or 4 doses during the course of the day, so administered doses represent only a small fraction of a tablet. Given that hydrocortisone is considered virtually insoluble in water and parents report variable levels of training in dose manipulation, variability in prepared dose is a concern. This was explored by Watson et al., International Journal of Pharmaceutics 545 (2018) 57–63 https://doi.org/10.1016/j.ijpharm.2018.04.054 Irrespective of whether patients are prescribed Alkindi in this situation, we are concerned that by not providing guidance on this point, an opportunity is being missed to support parents and caregivers in administration of	Thank you for your comment. As noted in response to another comment, the different formulations in the unit cost table for children was illustrative to allow the committee to consider different costs in the absence of health economic evidence. These were based on the different approaches taken in current practice according to the committee. There was no evidence specifically comparing different formulations in children (alkindi granules versus crushing and dispersing or pill splitting). The reference you provide does not meet the protocol of this review question. As stated in the committee discussion of the evidence the committee did not specify which approach to take in the recommendation due to the lack of comparative evidence. **Therefore, no recommendation was made advising people to crush tablets, nor was a recommendation made stating this should not be done.**

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				accurate HC doses to young patients. Same comments apply to Evidence review F Table 8.	
Diurnal Ltd	Evidence Review F	037	017	Merke 2021 *J Clin Endocrinol Metab. . 2021 Apr 23;106(5):e2063-e2077*. was downgraded due to the standard therapy comparator being more intensive than normal practice. This should be considered as suggesting that the difference between modified release hydrocortisone and standard care would be more marked in clinical practice, as was in fact found when the open label element of the study was compared to the literature.	Thank you for your comment. Downgrading due to indirectness has been removed and a footnote about the comparator being more intensive than usual practice has been added. GRADE ratings changed from very low to low and one rating from low to moderate. The 'committee discussion of the evidence' section has been edited accordingly but there was no impact of these changes on decision making or the recommendations.
Diurnal Ltd	Evidence Review F	039	042	It is surprising that there is a comment "percentage of patients with adrenal crises showed no clinically important difference between the groups". The difference for this life-threatening event in a RCT was 3 vs 0 or 9.8 per 100 patient years versus 0 per 100 patient years. We suggest that reference is made to th39is difference in adrenal crises as clinically important events.	Thank you for your comment. In our guidelines' methods, the assessment of clinical benefit/harm is based on the point estimate of absolute effect and a threshold of 50 per 1000 (please see methods chapter). The absolute risk difference with modified release hydrocortisone was 43 fewer per 1,000 and hence was deemed not to be a clinically important benefit. In addition, the confidence interval did not cross this threshold but crossed the line of no effect *(49 fewer to 13 more)*. Therefore, indicating the potential for 13 more crises which further increased the uncertainty. Please be assured that this is not the only criteria taken into account when making a decision about recommending a particular intervention. The certainty of the evidence using GRADE and taking all other outcomes into account meant that the committee could not make a

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					strong recommendation in favour of modified release hydrocortisone.
Diurnal Ltd	Guideline	General	General	Clearly Adrenal Insufficiency occurs only in classic CAH, but terminology in the guideline does not distinguish between classic and non-classic CAH	Thank you for your comment. The scope of the guideline covers people with Adrenal Insufficiency and does not focus on underlying causes.
Diurnal Ltd	Guideline	009	010	Table 2 The table states that modified release hydrocortisone can be considered as an alternative glucocorticoid in CAH patients aged 16 and over who have stopped growing, in doses of 20-30mg. These doses are inconsistent with international guidelines suggesting 15-25 mg be used(Speiser 2018 JCEM), and general practice that lower dosing should be used where possible with steroid replacement. Further, international guideline recommendations on the avoidance of long-acting more potent GCs to reduce risk of growth suppression, are based on data for synthetic GC, so specific avoidance of modified-release hydrocortisone in this setting is not evidence-based. Efmody is licensed from 12 years and over.	Thank you for your comment. The dosages have been removed for modified release hydrocortisone. Guidance on dosages is available in the BNF or summary of prescribing characteristics. . In the guideline it has now been clarified if the recommendations refer to tablets or capsules to distinguish between the two modified release hydrocortisone medicines. Where a recommendation is off label this highlighted. The reference you cite has been checked and although it does give a dose of 15-25mg it also reports there is no evidence to support this and practice varies. The committee agree in practice the lowest dose should be used. The committee is not aware of any good evidence on growth suppression using modified release hydrocortisone. Therefore, the group did not think it was appropriate to change current practice of avoidance until growth has stopped.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Diurnal Ltd	Guideline	009	010	Table 2 The table refers to modified-release hydrocortisone as alternative GC in both CAH and non-CAH PAI, and secondary and tertiary AI in patients aged 16 and over. No guidance is given regarding the different authorised indications and posology of the 2 modified release HC products.	Thank you for your comment. NICE guidelines do not routinely refer to specific drug names in recommendations. In this guideline the committee have looked at the different formulations and classes. Both medicines are referred to as modified-release hydrocortisone in the BNF. In the guideline it has now been clarified if the recommendations refer to tablets or capsules to distinguish between the two modified release hydrocortisone medicines. In addition, where a recommendation is off label this has been highlighted in the table. This table has been edited and instructions for dosing of modified release hydrocortisone is available in the BNF or SmPC.
Diurnal Ltd	Guideline	009	010 – 011	Table 2 Steroid replacement for AI in people aged 16 years and over. There is a mismatch vs age indications for current licenced branded products which split between paeds (<18) and adults (18+). Should there be a clearer distinction between adult and paediatric age ranges to align?	Thank you for your comment. The committee agreed the age cut-off for adult dosages as 16 years and over. Prescribers would need to consult the BNF or SPC for details on specific branded products. In the guideline it has now been clarified if the recommendations refer to tablets or capsules to distinguish between the two modified release hydrocortisone medicines. In addition, where a recommendation is off label this has been highlighted in the table.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Diurnal Ltd	Guideline	009 – 010	010	In table 2 We are concerned that the terminology "modified-release hydrocortisone" doesn't create a clear distinction between Efmody (hydrocortisone modifed-release hard capsules, authorised for treatment of CAH in children aged 12 and over and adults) and Plenadren (hydrocortisone modified-release tablets, authorised for treatment of AI in adults).	Thank you for your comment. NICE guidelines do not routinely refer to specific drug names in recommendations. In this guideline the different formulations and classes were looked at. Both medicines are referred to as modified-release hydrocortisone in the BNF. However, in the guideline it has now been clarified if the recommendations refer to tablets or capsules to distinguish between the two modified release hydrocortisone medicines. In addition, where a recommendation is off label this has been highlighted in the table. This table has been edited and for dosing of modified release hydrocortisone this is available in the BNF and SPC.
Diurnal Ltd	Guideline	011	001	In table 3 We are concerned that the terminology "modified-release hydrocortisone" doesn't create a clear distinction between Efmody (hydrocortisone modifed-release hard capsules, authorised for treatment of CAH in children aged 12 and over and adults) and Plenadren (hydrocortisone modified-release tablets, authorised for treatment of AI in adults).	Thank you for your comment. NICE guidelines do not routinely refer to specific drug names in recommendations. In this guideline the different formulations and classes were looked at. Both medicines are referred to as modified-release hydrocortisone in the BNF. However, in the guideline it has now been clarified if the recommendations refer to tablets or capsules to distinguish between the two modified release hydrocortisone medicines. In addition, where a recommendation is off label, this has been highlighted in the table. This table has been edited. For instructions on dosing of modified release hydrocortisone, please see the BNF or SmPC.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Diurnal Ltd	Guideline	011	004 – 005	If treatment options for CAH are included as part of the guidelines and in the table above, then it is inaccurate to state 'For multiple daily doses, give the larger dose in the morning and the smaller in the evening, mimicking the normal diurnal rhythm of cortisol secretion' as for Efmody the largest dose is given in the evening (see SmPC). A distinction is needed between Efmody and all other hydrocortisone formulations to clarify this, and avoid a potential patient safety issue.	Thank you for your comment. This has been noted and the sentence edited to state this refers to immediate release hydrocortisone. Guidance on prescribing is available in the BNF and SmPC. In the guideline it has now been clarified if the recommendations refer to tablets or capsules to distinguish between the two modified release hydrocortisone medicines. In addition, where a recommendation is off label this has been highlighted in the table.
Diurnal Ltd	Guideline	011	006	It would be useful to add some advice about the importance of starting cortisol before thyroid replacement in secondary Adrenal Insufficiency to avoid precipitating crisis.	Thank you for your comment. This guideline's focus is on Adrenal Insufficiency. The management of underlying conditions is not within the scope of this guideline. The tables include a footnote to refer to the BNF or BNFC for appropriate use and dosing in specific populations.
Diurnal Ltd	Guideline	012	001	Table 4 We feel that Alkindi should be exclusively mentioned here as the only therapy licenced at an appropriate dose in this age profile.	Thank you for your comment, however NICE guidelines do not routinely refer to specific drug names in recommendations.
Diurnal Ltd	Guideline	015	011	Given the issues that patients still relate with getting appropriate support during adrenal crisis, it is surprising that endocrine support is only to be thought about and not recommended when faced with a patient in adrenal crisis.	Thank you for your comment. This has been changed to 'seek endocrinology specialist advice'.
Diurnal Ltd	Guideline	016	007	The guideline doesn't mention that Efmody has a warning in the label that contraceptive advice should be	Thank you for your comment. Advice on using modified release hydrocortisone is available in the BNF and summary of prescribing characteristics.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				given due to the finding of improved fertility in patients with CAH (see Efmody SmPC)	
Diurnal Ltd	Guideline	022	021	The guideline suggests patients able to self-manage may need less frequent follow up- however some evidence suggests these patients may be at higher risk of crisis. eg. *Hahner S, Spinnler C, Fassnacht M, Burger-Stritt S, Lang K, Milovanovic D, Beuschlein F, Willenberg HS, Quinkler M, Allolio B. High incidence of adrenal crisis in educated patients with chronic Adrenal Insufficiency: a prospective study. J Clin Endocrinol Metab. 2015 Feb;100(2):407-16. doi: 10.1210/jc.2014-3191. Epub 2014 Nov 24. PMID: 25419882.*	Thank you. Although no evidence meeting inclusion criteria was found, the committee made consensus recommendations based on their experience. The frequency of clinical reviews will vary depending on the person's needs and the type of Adrenal Insufficiency they have. Adults who are confident with self-management and have stable clinical needs may require less frequent monitoring.
Diurnal Ltd	Guideline	023	017	Box 1 We recommend additional wording regarding accelerated growth in early childhood be added to the following 'Additional signs and symptoms to monitor in children and young people include faltering growth and early puberty.'	Thank you for your comment. This has been amended to 'abnormal growth rate and timing of puberty'.
Diurnal Ltd	Guideline	025	010	The guideline appears to recommend bone age monitoring for all AI patients, should this be clarified to refer only to CAH?	Thank you for your comment. Bone age monitoring is recommended in children and young people who are still growing.
Diurnal Ltd	Guideline	028	021 – 022	*The supporting document 'Rationale for drug doses' and the literature listed below suggest an expansive range in daily hydrocortisone production rates in healthy individuals, but the guideline document states a single daily physiological replacement dose in adults of 15 mg/day. We recommend stating that this is likely a*	Thank you for your comment. An individual treatment is advised, and the committee has provided dosage ranges in the tables and the terms used section, and has advised that the optimum daily dose is determined on the basis of clinical response.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				range rather than a single figure and an individualised treatment approach is advised. *Brandon DD, Isabelle LM, Samuels MH, Kendall JW, Loriaux DL. Cortisol production rate measurement by stable isotope dilution using gas chromatography-negative ion chemical ionization mass spectrometry. Steroids. 1999;64(6):372-378.* *Esteban NV, Loughlin T, Yergey AL, et al. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. J Clin Endocrinol Metab. 1991;72(1):39-45.* *Linder BL, Esteban NV, Yergey AL, Winterer JC, Loriaux DL, Cassorla F. Cortisol production rate in childhood and adolescence. J Pediatr. 1990;117(6):892-896.* *Caetano CM, Malchoff CD. Daily Glucocorticoid Replacement Dose in Adrenal Insufficiency, a Mini Review. Front Endocrinol (Lausanne). 2022;13:897211.* *Coursin DB, Wood KE. Corticosteroid supplementation for Adrenal Insufficiency. JAMA. 2002;287(2):236-240.* *Oprea A, Bonnet NCG, Polle O, Lysy PA. Novel insights into glucocorticoid replacement therapy for pediatric and adult Adrenal Insufficiency. Ther Adv Endocrinol Metab. 2019;10:2042018818821294.* *Husebye ES, Pearce SH, Krone NP, Kampe O. Adrenal Insufficiency. Lancet. 2021;397(10274):613-629.*	

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Kerrigan JR, Veldhuis JD, Leyo SA, Iranmanesh A, Rogol AD. Estimation of daily cortisol production and clearance rates in normal pubertal males by deconvolution analysis. J Clin Endocrinol Metab. 1993;76(6):1505-1510. *Kraan GP, Dullaart RP, Pratt JJ, Wolthers BG, Drayer NM, De Bruin R. The daily cortisol production reinvestigated in healthy men. The serum and urinary cortisol production rates are not significantly different. J Clin Endocrinol Metab. 1998;83(4):1247-1252.* *Purnell JQ, Brandon DD, Isabelle LM, Loriaux DL, Samuels MH. Association of 24-hour cortisol production rates, cortisol-binding globulin, and plasma-free cortisol levels with body composition, leptin levels, and aging in adult men and women. J Clin Endocrinol Metab. 2004;89(1):281-287.* *Ahmed S, Soliman AT, Ramadan MA, et al. Long-term prednisone versus hydrocortisone treatment in children with classic Congenital Adrenal Hyperplasia (CAH) and a brief review of the literature. Acta Biomed. 2019;90(3):360-369.*	
Diurnal Ltd	Guideline	029	001 – 002	The supporting document 'Rationale for drug doses' and the literature listed below suggest an expansive range in daily hydrocortisone production rates in healthy individuals, but the guideline document states a single daily physiological replacement dose in babies, children and young people under 16 years of 8 mg/m^2/day. We	Thank you for your comment. An individual treatment is advised, and the committee have provided dosage ranges in the tables, the terms used section, and have advised that the optimum daily dose is determined on the basis of clinical response.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				recommend stating that this is likely a range rather than a single figure and an individualised treatment approach is advised. *Brandon DD, Isabelle LM, Samuels MH, Kendall JW, Loriaux DL. Cortisol production rate measurement by stable isotope dilution using gas chromatography-negative ion chemical ionization mass spectrometry. Steroids. 1999;64(6):372-378.* *Esteban NV, Loughlin T, Yergey AL, et al. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. J Clin Endocrinol Metab. 1991;72(1):39-45.* *Linder BL, Esteban NV, Yergey AL, Winterer JC, Loriaux DL, Cassorla F. Cortisol production rate in childhood and adolescence. J Pediatr. 1990;117(6):892-896.* *Caetano CM, Malchoff CD. Daily Glucocorticoid Replacement Dose in Adrenal Insufficiency, a Mini Review. Front Endocrinol (Lausanne). 2022;13:897211.* *Coursin DB, Wood KE. Corticosteroid supplementation for Adrenal Insufficiency. JAMA. 2002;287(2):236-240.* *Oprea A, Bonnet NCG, Polle O, Lysy PA. Novel insights into glucocorticoid replacement therapy for pediatric and adult Adrenal Insufficiency. Ther Adv Endocrinol Metab. 2019;10:2042018818821294.* *Husebye ES, Pearce SH, Krone NP, Kampe O. Adrenal Insufficiency. Lancet. 2021;397(10274):613-629.*	

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
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Imperial College Healthcare NHS Trust	Evidence Review F	034	026	Section 1.1.15 It is worth noting that there is no current evidence for the use of Plenadren in CAH (as detailed in Table 17 of the supporting documentation F). We would suggest removing this to avoid confusion.	Thank you for your comment. The unit cost of Plenadren was included for completeness as it is an option for glucocorticoid replacement in CAH. In the guideline it has now been clarified if the recommendations refer to tablets or capsules to distinguish between the two modified release hydrocortisone medicines.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				It is also worth noting that prednisolone and Plenadren have the same plasma pharmacokinetic profile (Choudhury et al, 2021 (https://doi.org/10.1530/ec-20-0473)), whereas Efmody has a different profile, and may have added benefits.	The recommendations for CAH were made based on the available clinical evidence and committee expert opinion. Unfortunately, the reference you have kindly shared does not meet our protocol for inclusion but has been shared with the committee for information.
Imperial College Healthcare NHS Trust	Evidence Review K	012	049 – 050	We are concerned that there is no evidence that increased dosing may prevent hospital admissions (Section 1.1.1.4 in evidence review K, lines 049 - 050). The suggestion that even one hospital admission being saved is not relevant. There is also a risk of future harm and healthcare burden; for example, a single high dose of glucocorticoid in the context of a mental health crisis may precipitate a steroid-induced psychosis.	Thank you for your comment. Edits have made to the 'committee's discussion of the evidence' section of the chapter, removing the reference to a hospital admission saving and more information was added that related to the impact of steroid on mood. Steroids can sometimes exacerbate a mental health crisis and this needs to be balanced with prescribing increased dosing of glucocorticoids.
Imperial College Healthcare NHS Trust	Guideline	009	010 – 011	Section 1.3 – Routine pharmacological management. Table 2 We are concerned that the nomenclature for secondary and tertiary Adrenal Insufficiency may confuse non-Endocrinologists and suggest re-labelling the column with 'secondary Adrenal Insufficiency'. There is no difference in the management of secondary or tertiary Adrenal Insufficiency as we do not routinely distinguish between CRH or ACTH failure. We also	Thank you for your comment. The committee thinks that clinicians treating people with Adrenal Insufficiency would know the distinction between secondary and tertiary AI. For non-specialists definitions are provided in the 'terms used in this guideline' section.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				suggest signposting to section 1.9 for the management of glucocorticoid-induced Adrenal Insufficiency.	
Imperial College Healthcare NHS Trust	Guideline	009	010 – 011	Section 1.3 – Routine pharmacological management. Table 2 We are concerned that the inclusion of congenital adrenal hyperplasia (CAH) within the table is confusing. We suggest creating a separate column within the table to clearly distinguish the management of CAH, highlighting the need to titrate the glucocorticoid replacement dose according to the adrenal androgens.	Thank you for your comment. A separate column for CAH has been created as suggested.
Imperial College Healthcare NHS Trust	Guideline	009	010 – 011	Section 1.3 – Routine pharmacological management. Table 2 The routine use of prednisolone for primary and secondary Adrenal Insufficiency should be given in a single dose rather than in 1-2 divided doses. This dose should be 3-4 mg rather than 3-5 mg, as 5 mg is a supraphysiological dose (https://doi.org/10.1530/ec-23-0097) and increases the risk of steroid-related adverse events. The role for giving divided doses of prednisolone can only be to suppress androgens in CAH or to prevent nocturnal hypoglycaemia in type 1 diabetes (T1D). All other patients should receive once daily treatment.	Thank you for your comment. Prednisolone administered in 1-2 divided doses has been removed from the table. No evidence meeting the inclusion criteria was found for Prednisolone and therefore the committee made recommendations on the dosage based on consensus. Thank you for providing the references to the studies on prednisolone administration. The systematic review for routine pharmacological management was aimed at identifying randomised controlled trials comparing the effectiveness of different pharmacological treatments. Therefore, the studies you've listed could not be included in the review.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				We have now published a few papers of our experience (in over 70 patients) demonstrating that the recommended physiological replacement dose of prednisolone should be 3-4 mg once daily (Smith et al, 2017 (https://doi.org/10.1530/ec-17-0257) Sharma et al, 2023 (https://doi.org/10.1530/ec-23-0097)). There is no basis for the suggestion that prednisolone should be given in multiple doses. By doing so, it increases the risk of overreplacement, especially as the AUC (or steroid exposure) of prednisolone from 2 mg BD is far higher than 4 mg OD (Williams et al, 2016 (https://doi.org/10.1373/jalm.2016.020206). This is referenced in your supporting documentation: *Rationale for drug doses used clinically in the management of Adrenal Insufficiency.*	
Imperial College Healthcare NHS Trust	Guideline	009	010 – 011	Section 1.3 – Routine pharmacological management. Table 2 We recommend distinguishing between the different formulations of modified-release hydrocortisone, as neither Plenadren (dual release hydrocortisone) nor Efmody/Chronocort (delayed release hydrocortisone) are mentioned by name within this guideline. The current use of modified release hydrocortisone refers to two distinct hydrocortisone formulations, which have notable differences and the current lack of distinction	Thank you for your comment. NICE guidelines do not routinely refer to specific drug names in recommendations. In this guideline the different formulations and classes have been looked at. Both medicines are referred to as modified-release hydrocortisone in the BNF. However, in the guideline it has now been clarified if the recommendations refer to tablets or capsules to distinguish between the two modified release hydrocortisone medicines. In addition, where a recommendation is off label this has been highlighted in the table.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				may be confusing, with potentially dangerous consequences.	This table has been edited. For instructions on dosing of modified release hydrocortisone, please see the BNF or SmPC.
Imperial College Healthcare NHS Trust	Guideline	016	003 – 005	Section 1.4.11 – Non-pharmacological management We would suggest updating the details of the steroid alert card. Since this was updated in 2020, it is no longer blue. We would suggest removing this to avoid confusion.	Thank you for your comment. Although the merging of red and blue cards is currently under discussion with the NHS Chief Medical Officer, this has not yet taken place and the blue steroid cards are currently still in use.
Imperial College Healthcare NHS Trust	Guideline	018 – 019, 042	010 – 018 001 – 022	Section 1.5 - Management during psychological stress Rational for recommendations We agree with the committee that there is no documented evidence of anyone having experienced an adrenal crisis due to psychological stress alone. Our concern is that glucocorticoids, once initiated, are often continued inappropriately long term, which in turn could result in an adverse event, such as a neck of femur fracture or deterioration in glucose control. It could also lower the threshold for when glucocorticoids are doubled, increasing the risk of adverse events. This may have particularly deleterious effects in individuals where there has been no evidence-base for the decision to start them i.e. for psychological stress. We would also be concerned that a single high dose of IV or IM hydrocortisone may also worsen a mental	Thank you for your comment. The committee hope that discussion at diagnosis of Adrenal Insufficiency will help in reducing any psychological stress or anxiety and prevent inappropriate use of glucocorticoids, and the recommendations on information and support for people with Adrenal Insufficiency will help with this. The committee discussed the wide variation in factors and events that could lead to psychological stress, and the variation in what people find stressful and how they react making it difficult to determine whether a person would be at risk of adrenal crisis because of psychological stress. This, and the lack of evidence is described in the committee discussion and rationale sections of the guideline. Whilst acknowledging the lack of evidence the committee decided by consensus that short-term sick day dosing of glucocorticoids may be considered an option.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				health crisis or precipitate steroid-induced psychosis (https://www.bbc.co.uk/news/uk-england-manchester-68769797.amp, accessed 15/04/2024). We therefore suggest that the lack of evidence to support pharmacological treatment dosing during psychological stress should be clearly stated within the guideline below the sub-heading for Pharmacological Management (below line 011). We suggest that non-pharmacological management (1.5.4) should come above the pharmacological treatment, and this should be limited to '*There is no evidence that increased glucocorticoids are of benefit*'.	
Imperial College Healthcare NHS Trust	Guideline	026	008 – 016	Section 1.9 – Management of glucocorticoid withdrawal Section 1.9.1 We suggest clearly distinguishing between a therapeutic (i.e. tapering the dose according to underlying disease activity and initially guided by underlying specialty) and a physiological or endocrine taper (i.e. management of glucocorticoid withdrawal and Adrenal Insufficiency), as the therapeutic taper will vary between specialties. We would suggest emphasising that a physiological daily dose of prednisolone 4 mg or less.	Thank you for your comment. The recommendations have been amended throughout this section to provide clarification between tapering according to an underlying condition and a physiological taper in the management of Adrenal Insufficiency.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Imperial College Healthcare NHS Trust	Guideline	026	017 – 021	Section 1.9.2 For prednisolone doses below 3 mg, we would recommend a reduction of 1 mg per week over 21 weeks, as per our published protocol (https://www.impendo.co.uk/prednisolone/prednisolone-withdrawal) as this would be simpler and clearer for patients and clinicians to follow rather than the 10% reduction suggested in the guideline.	Thank you for your comment. The committee agrees that simplifying the recommendation is beneficial and has amended it to follow the Imperial Centre for Endocrinology prednisolone withdrawal regimen.
Imperial College Healthcare NHS Trust	Guideline	027	017 – 023	Section 1.9.7 We would not advocate doubling the physiologically equivalent glucocorticoid dose '*until symptoms resolve*' as these symptoms are expected and may persist. We would be concerned about prolonged use of double physiological glucocorticoid doses. We also suggest recognising that the symptoms of glucocorticoid withdrawal syndrome are indistinguishable from Adrenal Insufficiency (https://doi.org/10.1093/ejendo/lvad073). We would suggest the use of a slower taper to mitigate these symptoms. We suggest adding a sentence to clarify the difference between sick day rules where patients will require a double physiological dose for up to three days and then resume tapering once well.	Thank you for your comment. The committee note there may be steroid withdrawal symptoms. The recommendation is based on extensive committee discussions. Please note the committee agree with your comment that if necessary to use a slower tapering regimen to mitigate symptoms. Sick day rules are covered elsewhere within the guideline.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Imperial College Healthcare NHS Trust	Guideline	027 - 028	024 – 028 001 – 011	Section 1.9.8. We suggest clarifying the physiological prednisolone dose patients should be taking prior to measuring a morning serum cortisol value, which should be 3-4 mg once daily rather than 5 mg as suggested. It is worth noting that 5 mg prednisolone is a supraphysiological dose. This will likely result in a low morning serum cortisol value of less than 300 nmol/L because of prolonged and persistent adrenal suppression. This can be avoided by only measuring a morning cortisol when the patient is taking a physiological dose of 3-4 mg. We would be concerned that individuals with a low serum cortisol due to the suppressive effects of prednisolone would be inappropriately restarted on replacement glucocorticoid, rather than continuing to be weaned off. We would also suggest advising patients to delay their morning dose of prednisolone until after the morning serum cortisol blood test is taken, rather than pausing for 24 hours, which may result in patients missing one day of prednisolone dosing.	Thank you for your comment. In terms used section, the committee have suggested the physiological dose as prednisolone 3mg/day to 5mg/day. These are the doses recommended before testing or tapering to withdraw prednisolone. The committee agreed the timings to pause glucocorticoids and then to restart after testing at the physiological equivalent dose.
Imperial College Healthcare NHS Trust	Guideline	029 – 030	025 – 028 001	We suggest clearly defining 'tertiary Adrenal Insufficiency' as 'glucocorticoid-induced Adrenal Insufficiency', rather than also including hypothalamic lesions as a cause for tertiary Adrenal Insufficiency within this definition.	Thank you for your comment. The definitions were agreed by the committee. The intention was to provide simplified definitions for the terms used in the guideline to aid non-specialists in understanding the recommendations.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Clinically, both pituitary and hypothalamic lesions are similar. There is no way of distinguishing between them, and they are managed identically. They should therefore both be included under the definition of 'secondary Adrenal Insufficiency'. The treatment for glucocorticoid-induced disease (withdrawal of glucocorticoids) is very different to the treatment of hypothalamic lesions (requiring life-long glucocorticoid replacement). The two should therefore not be defined in the same way.	
Imperial College Healthcare NHS Trust	Question	1		One of the challenges is ensuring that other medical specialties are aware of the guidelines in optimal methods of steroid withdrawal. We suggest engaging national organisations such as the Royal College of Physicians (RCP) and specific specialty organisations such as the British Association of Dermatologists and British Society of Rheumatology to help disseminate the guidelines. We would also suggest an editorial in a widely read general medical journal such as the British Medical Journal (BMJ). We would be happy to be involved in writing this.	Thank you for your comment. NICE are engaging with all stakeholders to ensure that various health care professionals particularly non-specialists are aware of the guideline. The committee will consider future publications and presentations to promote the guideline.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Imperial College Healthcare NHS Trust	Question	2		Confusion may arise by references to use of modified release hydrocortisone in table 2, section 1.3. We note the cost for modified release hydrocortisone is given in the supplementary evidence, but this is not clear in the guideline.	Thank you for your response. In the guideline it has been clarified if the recommendations refer to tablets or capsules to distinguish between the two modified release hydrocortisone medicines. In addition, where a recommendation is off label this has been highlighted in the table.
Imperial College Healthcare NHS Trust	Question	3		We suggest lowering the serum cortisol cut-off values to: Below 100 nmol/L (from 150 nmol/L) for starting management for Adrenal Insufficiency. Between 101 – 200 nmol/L to refer the person to endocrinology or arrange a short Synacthen test (and discuss abnormal results with endocrinology). Above 201 nmol/L – recognise that Adrenal Insufficiency is very unlikely. There is evidence to suggest that a random serum cortisol of >200nmol/L is associated with 100% recovery of the HPA axis at four years in patients with potentially reversible causes of Adrenal Insufficiency (e.g. pituitary surgery and glucocorticoid-induced Adrenal Insufficiency). (Pofi et al, 2018 (https://doi.org/10.1210/jc.2018-00529)).	Thank you for your response. The committee considered your suggestions and the recommendations have been revised in light of comments from stakeholders, and the consensus of the committee based on their experience and knowledge of current practice.
Imperial College Healthcare NHS Trust	Question	4		In section 1.3 we suggest updating the doses of prednisolone to 3-4 mg once daily, and to clarify which modified release hydrocortisone formulation should be	Thank you for your response.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				used in the management of primary Adrenal Insufficiency compared with congenital Adrenal Insufficiency (CAH). In sections 1.4.2 -1.4.3, we would recommend doubling the physiological replacement glucocorticoid dose (e.g. doubling 3 mg prednisolone to 6 mg or 4 mg to 8 mg once daily as a maximum daily dose) rather than a blanket minimum dose of 10 mg. Similarly, we would recommend doubling the individual's normal replacement hydrocortisone dose (e.g. 10mg/5mg/2.5mg to double to 20mg/10mg/5mg) whilst acutely unwell. There is no evidence that the minimum hydrocortisone dose should be 40 mg. Excess glucocorticoid exposure at times of sepsis may further suppress the immune system with potentially negative consequences.	- The dose of prednisolone of 3-5mg was agreed upon based on committee consensus. - For modified release hydrocortisone, in the guideline it has been clarified if the recommendations refer to tablets or capsules to distinguish between the two modified release hydrocortisone medicines. In addition, where a recommendation is off label this has been highlighted in the table. - For sick day dosing, the committee recommended an increase to at least 40 mg a day because if someone is on hydrocortisone 2-3 times a day doubling the dose may not give sufficient rise in cortisol to cover acute physiological stress over a 24-hour period. In addition, some people are on a low dose such as 5mg three times a day and again doubling does not give sufficient 24-hour cover. Therefore, the committee agreed that for hydrocortisone the recommendation is 10mg four times a day. Similarly for prednisolone, some people may be on 3mg daily and doubling the dose would not be sufficient, which is why the committee recommended 5mg twice daily. A key part of sick day rules advice is to reduce glucocorticoids when physiological stress is resolving so as to reduce

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					the time to the shortest period of 'increased glucocorticoid dosing'
Imperial College Healthcare NHS Trust	Question	5		Yes, we agree with this approach.	Thank you for your response.
Imperial College Healthcare NHS Trust	Question	6		We suggest clearly distinguishing between a therapeutic taper (i.e. tapering the dose according to underlying disease activity and initially guided by underlying specialty) and a physiological or endocrine taper (i.e. management of glucocorticoid withdrawal and Adrenal Insufficiency). The former should be the responsibility of the treating medical speciality. We suggest a more practical weaning protocol that we have been using clinically since 2018 (https://www.impendo.co.uk/prednisolone/prednisolone-withdrawal). We do not agree with doubling the dose in patients who show symptoms of Adrenal Insufficiency.	Thank you for your response. The recommendations have been amended throughout this section to provide clarification between tapering according to an underlying condition and a physiological taper in the management of Adrenal Insufficiency.
Medics 4 Rare Diseases	EIA	002		Age There could be more specific guidance on Transition of Care – the process of which is recommended to start at 11 based on the Ready Steady Go guidelines. You mention vulnerable children where the condition is not being managed adequately. I would like to see recognition that when treatment is refractory to review diagnosis – is there an underlying genetic condition that has not been picked up.	Thank you for your comment. The committee agreed the recommendations in the existing guideline 'Transition from children's to adult services for young people using health or social care services' were appropriate to cross-refer to. The guideline recommends transition support should be when it is developmentally appropriate, and with regard

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Disability The guideline could make stronger statements to ensure that education is provided to a carer as someone may lose capacity in a crisis and be reliant on a loved one. With regards to mental health - the multiple mentions of patient support groups is excellent. We do find that HCPs are not well-equipped to use these important support groups so more detailed guidance might help them. Or suggested groups.	to timing from year 9 as stated within the Children and Families Act 2014. Management of underlying conditions are not within the scope of this guideline. The guideline includes recommendations on giving information to people with Adrenal Insufficiency, families, and carers on what to do in emergency situations and how to administer glucocorticoids and seek medical advice. This is described in the committee discussion in Evidence review A. The committee also decided to refer to the NICE guidance on Supporting adult carers and young carers for generic recommendations on information and support for carers. Links to organisations that provide advice and support to people with Adrenal Insufficiency and family and carers will be made available on the NICE website on publication of the guideline.
Medics 4 Rare Diseases	EIA	003		There is an equality issue based on skin colour: One of two main principles for suspecting Adrenal Insufficiency is hyperpigmentation and the other is a list of systemic symptoms. Recognition of dermatological changes in skin of colour is underrepresented in clinical education and research. This needs to be taken into account as people of colour	Thank you for your comment. We have added to the recommendation and the rationale and impact section that this feature may not be easily recognised in people with Black or Brown skin and that clinicians should inspect buccal mucosa and surgical scars and ask the person if they have noticed any change to their skin.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				may not have hyperpigmentation recognised for what it is. There is an equality issue based on the condition potentially being invisible: Our members report not being listened to or believed and being fearful of how they will be treated because their condition is invisible.	
Medics 4 Rare Diseases	EIA	003	3.4	I believe these guidelines could disadvantage people of colour due to the causes stated above. The statement on Page 4 Line 3 of the Guideline about people living active and full lives are over-simplistic and could isolate those who have Adrenal Insufficiency as part of a syndrome, those who are less able to self-manage and those who don't live near specialist services. Someone's ability to live their life to the fullest with a long-term condition is reliant on many different factors and such sweeping statements can lead to blame and shame for those who face challenges or struggle.	Thank you for your comment. The Guideline committee agreed that if people with Adrenal Insufficiency are provided with information and support, it is possible for them to lead full and active lives. The committee includes lay members who live with the condition and who have contributed to the development of this guideline to ensure a balanced view that reflects the lived experience is represented.
Medics 4 Rare Diseases	EIA	003	3.5	The statement on Page 4 Line 3 of the Guideline about people living active and full lives are over-simplistic and could isolate those with a disability.	Thank you for your comment. The Guideline committee agreed that if people with Adrenal Insufficiency are provided with information and support it is possible to lead full and active lives. The committee includes lay members who live with the condition and who have contributed to the development

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					of this guideline, to ensure a balanced view that reflects the lived experience is represented.
Medics 4 Rare Diseases	EIA	003	3.6	We recommend taking into account the comments provided on the Guidelines regarding looking for dermatological signs in people of colour; suspecting rare genetic conditions; wording around living a full and active life.	Thank you for your comment. We have clarified in the recommendation and the rationale section that hyperpigmentation may not be easily recognised in people with black or brown skin colour and added to the Committee discussion of the evidence (section 1.1.9.3 evidence review B) that clinicians should inspect buccal mucosa, surgical scars, and ask the person if they have noticed any change to their skin.
Medics 4 Rare Diseases	Guideline	General	General	We are grateful for the opportunity to provide consultation on this topic as Adrenal Insufficiency is a condition that Medics4RareDiseases uses a lot as an example of how conditions may be rare but need a high level of suspicion to prevent death and disability. A number of M4RD's Ambassadors live with or have a family member with Adrenal Insufficiency either from Addison's or another rare cause. We welcome the collaboration with patient support groups and the multiple mentions of them as a source for support and would like to see this as a	Thank you for your comments. The guideline recommends carrying steroid emergency cards and use of other forms of medical alerts, the use and sharing of management plans and guidance on emergency management of adrenal crisis including training for people and their carers on how to use emergency kits. The hope is that this guidance will help prevent the situations you describe from occurring in the future.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				recommendation of support for both HCP and patient/carer. The main fears our Ambassadors have is that their condition is invisible and there is no robust way on NHS systems to make sure that if they deteriorate as an inpatient or waiting in acute services the potential risk of their condition will be recognised. One of our Ambassadors puts up her own warning signs on the wall with information by her bed in case someone doesn't understand her condition. She has also slept with a piece of a paper in her hand which tells any HCP about her condition and how to recognise deterioration or what to do. They report that this is a particular worry since health records have gone online and alerts are not robust enough. Another major concern is about young people in crisis being given information and education while alone and then their families not knowing what was said or what to do in a crisis. Therefore we recommend that all patient education is done in the presence of another individual.	

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				For lived experience recommendations on this please refer to: Patient Ambassador living with Addison's https://www.buzzsprout.com/1875024/13939130-how-a-medical-student-saved-my-life-and-my-experience-of-addison-s-disease-with-corrinne-hepworth.mp3?download=true Medical Student Ambassador whose brother was diagnosed with Addison's https://www.buzzsprout.com/1875024/11489473-dr-grace-brother-eddie-addison-s-disease-and-ed.mp3?download=true Mother whose twin sons received a delayed diagnosis of Adrenoleukodystrophy https://www.buzzsprout.com/1875024/10395411-lifelines-in-leukodystrophy-a-supportive-gp-and-peer-support.mp3?download=true	
Medics 4 Rare Diseases	Guideline	General	General	Final general comments from Member living with Addison's Disease:	Thank you for your comment. Guidance on sick day dosing, management of psychological stress and tapering glucocorticoids are covered within the guideline. A person with Adrenal

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Standard sick dosing may not be appropriate, following emergency dosing/ severe illness. Consider triple dosing, rather than double dosing, gradual tapering to avoid deterioration. Patient distress or re-occurence of symptoms should be heeded and secondary checks / advice sought. Do not refuse hydrocortisone to person who has known Adrenal Insufficiency. Adrenal crisis / instability impacts upon mental function, consider additional support / advocacy according to patient	Insufficiency may have individual needs requiring a different approach and this would be agreed between the person and their clinical team.
Medics 4 Rare Diseases	Guideline	003	013	It is important to emphasise that a clinical diagnosis might be made at the time of a crisis or the patient feeling unwell in an acute setting. Our members repeatedly report being delivered news and information while on their own at a time when they are too unwell to understand, retain and communicate it. Therefore our advice is to separate this section into e.g. "Diagnosis at time of Crisis" and "Patient and carer education soon after diagnosis". Recommend that the patient is with a nominated carer who would spot signs of deterioration and step in when the patient is unable to care for themselves. Education	Thank you for your suggestion. Information and support should be tailored according to the needs of the person, and this is covered at both the time of diagnosis in the information and support section and in the non-pharmacological management of physiological stress sections of the guideline.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				should be given in a quiet space with time for questions and appropriate support to be provided. Offer written (or other preferred format) information, and opportunity for a follow up visit to re-discuss when they are feeling more well	
Medics 4 Rare Diseases	Guideline	003	018	To include how to set up ambulance alert locally - often missed and vital if ambulance service called when person is unconscious.	Thank you for your comment. A recommendation on how to setup medical alerts is included in the guideline.
Medics 4 Rare Diseases	Guideline	003	019	We have found that HCPs don't often refer to patient support groups – could this recommendation be more specific e.g. mention Addison's Disease Self Help Group.	Thank you for your comment. Links to organisations who provide advice and support will be made available on the NICE website on publication of the guideline.
Medics 4 Rare Diseases	Guideline	004	003	The statement *"people that having Adrenal Insufficiency does not prevent living 4 a full and active life"* is false". We think this statement is misleading to HCPs and potentially harmful to patients. It could lead to false assurances made by HCPs and therefore patients and families not receiving appropriate care. Adrenal Insufficiency is life-threatening if not managed correctly. There are conditions in which Adrenal Insufficiency is one part of a syndrome that is life-limiting. And for some the diagnosis does prevent living the same life as before. We think this statement is misleading to HCPs and potentially harmful to patients.	Thank you for your comment. The Guideline committee agreed if people with Adrenal Insufficiency are provided with information and support it is possible to lead full and active lives. The committee includes lay members who live with the condition and who have contributed to the development of this guideline, to ensure a balanced view that reflects the lived experience is represented. Recommendations on information provision during periods of sickness or adrenal crisis are in the non-pharmacological management during physiological stress section of the guideline.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				"Reassure people who live with Adrenal Insufficiency that they can be supported to live well". The divide this section into "Living well" and "Managing in crisis" (or something of that ilk)	
Medics 4 Rare Diseases	Guideline	004	007	This statement is contradictory to the opening statement and it's important to stress that Adrenal Insufficiency can be life threatening unless managed properly. However when managed properly people can be supported to live well and achieve a good quality of life.	Thank you for your comment. The committee don't agree this is contradictory with the opening statement. Providing information on a person's treatment is to support the person in self-managing their condition and help keep them safe.
Medics 4 Rare Diseases	Guideline	004	013	Please add information about screening that may be required.	Thank you for your comment. Further information is provided in the ongoing care and monitoring section and a link to this has been added.
Medics 4 Rare Diseases	Guideline	005	002	A management plan should include psychosocial support including peer support and methods for proactively looking after mental health	Thank you for your comment. The management plan would need to be developed by the health professionals delivering the care with the patient and be tailored to the needs of the individual.
Medics 4 Rare Diseases	Guideline	005	017	Excellent point. Can you go one step further and recommend the HCP themselves engages with Patient Support Groups and makes specific suggestions about resources of support that might benefit the patient e.g online workshop or family conference. Encourage carers to seek support from Advocacy Groups even if the patient doesn't wish to do so. Recognise impact on carers and those around the patient.	Thank you for your comment. NICE guidance does not usually specify how services are delivered as this would be determined locally based on clinical need.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Medics 4 Rare Diseases	Guideline	005	020	People supporting the person may not officially meet the threshold for 'carer's assessment'. But may still benefit from the support provided by advocacy groups. Recognise the impact of diagnosis on those around the person.	Thank you for your comment. The committee has included recommendations on other sources of information and advice for families and carers and relevant support groups and charities that would offer support to people providing care and assistance to a person with adrenal insufficiency.
Medics 4 Rare Diseases	Guideline	006	003	Start this section with "There are a number of causes of Adrenal Insufficiency and it may be part of a syndrome. It may be an invisible condition or classical symptoms such as hyperpigmentation might be underrecognized on different skin types. Therefore have a high level of suspicion in the presence of signs or features:…."	Thank you for your suggestion. The identification of Adrenal Insufficiency and the range of signs, symptoms and features observed is discussed in the committee discussion section of Evidence review B. Clarifications in the recommendation and the rationale section have been added that hyperpigmentation may not be easily recognised in people with black or brown skin colour and added to the Committee discussion of the evidence (section 1.1.9.3 evidence review B) that clinicians should inspect buccal mucosa, surgical scars and ask the person if they have noticed any change to their skin.
Medics 4 Rare Diseases	Guideline	006	015	Under lethargy please add specifics: excessive need for sleep (18 hours plus per day) adverse/ heightened reaction to stress	Thank you for your comment. The committee thinks the wording is clear. The recommendation qualifies that the clinician should consider whether there is any other clinical explanation or if the symptom is persistent before suspecting Adrenal Insufficiency in a person.
Medics 4 Rare Diseases	Guideline	007	014	ADD "Think about the possibility of Adrenal Insufficiency in people with an underlying genetic condition with signs and symptoms above" – the aim is to prevent Adrenal Insufficiency being missed and not treated because of a	Thank you for your comment. Underlying conditions are outside of the scope of this guideline.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				genetic diagnosis and lack of awareness of how they might interlink e.g. leukodystrophy	
Medics 4 Rare Diseases	Guideline	008	001	Table 1 - Query: Will these values for cortisol levels needs to align with the current guidance on NICE CKS guidelines for Addison's, or whether the CKS ones will be updated to reflect this? Just that the values in this interpretation are different so may lead to confusion when clinicians are trying to interpret and decide how to manage e.g CKS states that if <100 hospital admission is advised https://cks.nice.org.uk/topics/addisons-disease/diagnosis/investigations-suspected-adrenal-insufficiency/	Thank you for your comment. The relevant Clinical Knowledge Summaries will be reviewed for any changes to align. recommendations at publication.
Medics 4 Rare Diseases	Guideline	008	003	ADD "inform the patient of why this is important so they ensure the test is booked at appropriate times"	Thank you for your comment. An explanation for the timing of serum cortisol tests is given in the rationale and impact section on initial investigations.
Medics 4 Rare Diseases	Guideline	009	001	Some part of this section needs to encourage regular review with patients about their symptoms, and how regularly they are needing to take extra doses - as this may need to trigger a review of their overall regular daily dosing.	Thank you for your comment. Reviews of people's symptoms and treatment is covered within the 'Ongoing care and monitoring' section of the guideline. The information and support recommendations also include providing information on how people can access clinical advice when needed.
Medics 4 Rare Diseases	Guideline	010	004	Recommendation directly from Member living with Addison's Disease: Consider circadian dosing to improve quality of life. Also consider increasing dose or adding additional dose at night time during periods	Thank you for your comment. Taking medication for Adrenal Insufficiency during periods when a person is unwell is covered within the management during physiological stress section of the

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				of being unwell, to prevent insufficient cover during night and aid in recovery process https://www.cahisus.co.uk/pdf/24%20HOUR%20PROFILE%20ASSESSING%20CORTISOL%20REPLACEMENT%20ADDISON'S.pdf https://cahisus.co.uk/pdf/EXTRA%20HYDROCORTISONE%20DOSE%20AT%204AM%20IN%20ILLNESS%20ADDISON%27S.pdf	guideline. Recommendations have also been made on providing information and advice on taking medication at different times of the times of day or night within the information and support section.
Medics 4 Rare Diseases	Guideline	013	003	Reassure the patient that there is no risk of "overdose" of hydrocortisone in a crisis situation. Taking more is less dangerous than underdosing.	Thank you for your comment. These recommendations refer to what should be included in an emergency kit. In the emergency management of adrenal crisis section the committee has included a recommendation confirming there is no risk of overdose from hydrocortisone in an emergency situation.
Medics 4 Rare Diseases	Guideline	013	004	Advise the person on the importance of carrying the kit with them at all times - including when driving (in case of accident etc.). Provide advice (or letter if necessary) on how to explain to restricted settings the need for the kit. (i.e. taking kit through the airport, or esp. for young people, taking the kit into a club/music venue - taking in a needle and fear of being challenged could be a big barrier to young people actually carrying their kit)	Thank you for your comment. The committee expects that this would be discussed at the time of prescription of the emergency kit or training. The information and support recommendations also provide advice on the importance of medication for adrenal crisis and having supplies of medicines at all times, including when travelling or when away from their usual residence.
Medics 4 Rare Diseases	Guideline	013	023	Recommend to signpost to patient advocacy group resources. Training should be given to patient and one	Thank you for your comment. A recommendation has been made to ensure people are trained on how to use

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				other who might need to attend the patient in times of crisis or illness. Provide education and support on emergency kits for people requiring them, and at least one significant other around them. Advise them on resources they can use to educate other people in their lives - often the person delivering the emergency kit will not be the person themselves (As they are ill at the time).	the kit. In the evidence review for emergency management, there is a detailed summary of the committee's discussion where they noted that carers, family members, or friends may also require training and that this could be done in a group setting. As these were primarily consensus-based recommendations the committee did not consider they could specify exactly who should receive training and how this should be delivered. This should be decided locally taking into account individual circumstances.
Medics 4 Rare Diseases	Guideline	013	025	Must give info on how to source the replacement. Pharmacies will provide the medication but not equipment e.g. syringes.	Thank you for your comment. This will need to be agreed locally.
Medics 4 Rare Diseases	Guideline	014	010	Directly from a member and doctor/carer with Addison's Disease: If on replacement of 25mg, double dose equates to 50mg (which should be the minimum) patients are often encouraged to minimally updose - which creates the wrong stigma/ behaviour and additional risk.	Thank you for your comment. Based on committee consensus they did not advocate doubling the dose but instead recommended a fixed increase to 10mh of hydrocortisone four times daily to mimic cortisol rise during physiological stress. They recommended that the dose should be reduced to the usual replacement dosage once the episode has been resolved. These are recommendations only and there could be individual circumstances where expert clinical judgment may be required on dosing during periods of physiological stress.
Medics 4 Rare Diseases	Guideline	014	020	Safety net to call for help if at any point they begin to feel systemically unwell after vomiting - better safe than sorry! Provide guidance on what to do if what	Thank you for your comment. The recommendations state that if vomiting recurs within 30 minutes of a

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				happens if they vomit 2 hours later or continue to deteriorate and symptoms escalate.	previous dose of oral glucocorticoid to use intramuscular hydrocortisone and to go to A&E.
Medics 4 Rare Diseases	Guideline	015	001	A patient may be able to absorb / take oral steroids but in the event of severe illness they may be unstable / require higher doses (which need to be administered and monitored) in a hospital setting. Re-peat crisis is common when patients are refused admission or sent home 'stable' without proper observation.	Thank you for your comment. The committee have recommended that a person should be admitted to hospital if during periods of physiological stress, they are unable to absorb oral glucocorticoids.
Medics 4 Rare Diseases	Guideline	015	006	Directly from a Member living with Addison's Disease: A patient recovering from a crisis event is likely to require higher dosing, without being septic or in ITC. Double dosing may not be sufficient, Triple dosing may be required. This is anecdotally evidenced within adrenal insufficient patients.	Thank you for your comment. The committee don't advise doubling dose but giving hydrocortisone 4-hourly. Some people may be on low dose and therefore doubling may not be enough.
Medics 4 Rare Diseases	Guideline	019	006	Great to see this recommendation. Can you give specific guidance on how to do this e.g. mention PAGs you've worked with because we find HCPs don't use these resources enough.	Thank you. No evidence was found to support any specific recommendations in this area. The committee decided to make consensus recommendations to provide advice on accessing information and support to help reduce stress and avoid an adrenal crisis. The committee acknowledged the importance of patient support groups and organisations in providing information and support. It is not possible to mention specific patient organisations within the guideline, but links to relevant patient organisations will be available from the NICE website on publication of the guideline.
Medics 4 Rare Diseases	Guideline	019	008	Please review this phrasing. It is a legal requirement for employers to make reasonable adjustments. The use of	Thank you. The wording of the recommendation has been revised.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				"any adjustments that could be made" doesn't really reflect this.	
Medics 4 Rare Diseases	Guideline	020	014	slurred speech visible shaking / twitching of arms, legs, involuntary spasms etc perceived anxiety/ depression	Thank you for your suggestions. The committee decided to focus on the features and symptoms most commonly seen.
Medics 4 Rare Diseases	Guideline	022	005	And review their need for psychosocial support, or further education on managing their condition	Thank you. The committee believes that reviewing a person's psychological well-being and how they manage their condition is covered in recommendation 1.8.6.
Medics 4 Rare Diseases	Guideline	022	016	Consider rephrasing because "at transition" is too late in the transition process. The Ready Steady Go Transition process suggests starting transition conversations at 11. We recommend adding reviews Guideline based on these guidelines as Transition of Care is major challenge to our membership. https://www.readysteadygo.net/home.html	Thank you for the reference. The recommendation has been amended to specify 'during transition', recognising that this process occurs over a lengthy period of time.
Medics 4 Rare Diseases	Guideline	029	008	This statement oversimplifies the causes of Primary Immunodeficiency. Although you can't list them all it's important to not embed a cognitive bias that will lead to diagnostic delay of rarer causes. Suggested rephrase: "Primary Adrenal Insufficiency is caused by disease in the adrenal glands themselves. Addison's disease is a common cause in young people and adults, congenital adrenal hyperplasia is a common cause in children. It is important to keep in mind that	Thank you for your comment. The definitions are simple descriptions to aid in understanding the guidelines particularly by non-specialist. It was noted there are multiple rare causes. However, this was not meant to be an exhaustive list.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				there are other rare conditions and syndromes that cause primary Adrenal Insufficiency." For example Adrenoleukodystrophy (ALD) is an important though rare cause of Adrenal Insufficiency which needs prompt diagnosis.	
Medics 4 Rare Diseases	Guideline	044	022	Be patient guided when adrenal crisis / insufficient cortisol is suspected. All symptoms discussed in diagnosis of primary Adrenal Insufficiency, can re-present when either insufficient replacement regime (for example if sickdosing required) or in acute adrenal crisis. Personal experience and wider patient experience (anecdotal) can be showing symptoms of and feeling symptoms of crisis, whilst initially presenting 'expected physiological markers', bp is shown to rise in some patients, and crisis escalate before the expected drop/ low BP is witnessed. Patients can quickly deteriorate (within minutes) and go into shock, without having diarrohea/ vomiting. Cortisol in blood tests is not necessarily representative of physiological demand during crisis or illness. Personal exp: I received multiple doses of	Thank you for your comment. The recommendations are guided by national and international guidelines, evidence, and committee experience, However, the committee agree that clinical judgement based on individual patient symptoms and medical history should also be considered.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				intramuscular hydrocortisone in quick succession, had the emergency standards not been exceeded, I'd likely not have survived.	
Medics 4 Rare Diseases	Guideline	045	025	Patients frequently experience life-threatening delays in receiving fluids and prescribed hydrocortisone on hospital wards, medication needs to be re-prioritised as urgent, same category as insulin, morphine etc Dosing is time-sensitive and this impacts management of symptoms/ condition and if not adhered to results in adverse outcomes.	Thank you for your comment. Recommendations 1.7.1 and 1.7.2 emphasise the need for immediate initiation of management during emergencies which when implemented should minimise delays in treatment and reduce adverse outcomes.
Medics 4 Rare Diseases	Guideline	046	018	Adverse outcomes result from lack of advocacy/awareness, and in many cases patient neglect. Delays and non compliance with protocols and medication needs result in lost lives. Encourage practitioners to be guided by patient experience and listen to patients (who are distressed or showing symptoms). Do not refuse cortisol replacement in patients who have a known diagnosis.	Thank you for your comment. The committee hopes this guideline will raise awareness of Adrenal Insufficiency and improve identification and management of the condition.
Medics 4 Rare Diseases	Question	5		In recommendation 1.4.8 and 1.4.9 we have directly cross referenced guidance produced by external organisations. We agree with this approach and would recommend the same for non-pharmaceutical management with external organisations such as Addison's Self Help Group's patient and carer	Thank you for your response. Links to other adrenal insufficiency patient groups and organisations where people can access further information and support will be made from the NICE website on publication of the guideline.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				information or the Ready Steady Go guidance on transition of care.	
NHS England	Guideline	General	General	The guidelines are mainly and appropriately relevant to provision of care by secondary care services. It would be good to highlight areas where primary care services could offer support for patients – for example considerations of care plans, implementation/support for monitoring and liaison with secondary care services.	Thank you for your comment. NICE guidance does not usually specify where care is provided as this is determined locally based on clinical need. Not all people with Adrenal Insufficiency would require secondary care services and would receive care from primary care with support from secondary care where needed.
PMR-GCA Scotland	Guideline	General	General	We welcome the document as a whole because our members often report that healthcare professionals within rheumatology seem to lack knowledge about this area of medicine.	Thank you for your comment. The committee are pleased that the guideline will be useful to healthcare professionals.
PMR-GCA Scotland	Guideline	General	General	We welcome protocols about when to suspect AI in patients reducing steroids after long-term use and when to refer for testing.	Thank you for your comment. The committee are pleased that you find the recommendations useful and helpful.
PMR-GCA Scotland	Guideline	019	006	We are pleased to see recognition of the importance of patient support groups and organisations which help to provide the information and support which is necessary for the self-management of our members' conditions.	Thank you for your comment, and for participating in the consultation process.
PMR-GCA Scotland	Guideline	027	005	We welcome the recommendation that patients should not be routinely switched from prednisolone to hydrocortisone since this often results in poor control of their rheumatological condition.	Thank you for your comment.
Royal College of General	Guideline	006	021	Rec 1.2.2 We are concerned that it is very difficult to correctly identify at risk patients opportunistically who have significant steroid exposure through both frequent	Thank you for your comment. The committee agrees it is difficult but the clinician should ask the person or their

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Practitioner (RCGP)				acute and or repeat prescription issues. Additionally, an increasing number of patients receive intra-articular steroid injections.	carer about their medication and any other conditions when carrying out an assessment.
Royal College of Nursing	Guideline	003	005	Employers also need to recognise requirement for emergency treatment	Thank you for your comment. A recommendation to discuss a diagnosis and treatment of Adrenal Insufficiency with employers is included in the information and support section of the guideline.
Royal College of Nursing	Guideline	005	005	We recommend considering the term including independent healthcare sectors for appropriate representation of the different clinical settings	Thank you for your comment. NICE guidance is commissioned and developed for use by healthcare providers delivering NHS services. Other independent providers may also find the guidance helpful.
Royal College of Nursing	Guideline	008	001	Table may imply that the short synacthen test can be ordered within general practice, at present requires endocrinology referral – may need to acknowledge this	Thank you for your comment. This has been removed from the recommendation.
Royal College of Nursing	Guideline	010	001	Consider moving abbreviation before the table to prevent confusion for readers	Thank you for your comment. CAH has been moved into a separate column and is labelled in full as well as in the footnote to the table.
Royal College of Nursing	Guideline	013	007	Concern around who is required to deliver this training, can often be confused between endocrinology and primary care – may be useful to identify where training should be delivered, as often practice nurses can be required to deliver training to parents without much information	Thank you for your comment. NICE guidance does not usually specify how services are delivered as this would be determined locally based on clinical need, available resources and clinical expertise.
Royal College of Nursing	Guideline	021	006	Recommendation needs to consider the appropriate language – not just a GP who the patient may speak too, consider primary care clinician or practitioner for inclusivity of possible nursing staff involved	Thank you The wording has been amended to advise going to the hospital in an ambulance without needing a referral.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Paediatrics and Child Health (RCPCH)	Guideline	General	General	Plasma ACTH is not useful test for follow up of central Adrenal Insufficiency.	Thank you for your comment. The guideline does not include recommendations on using plasma ACTH for follow up of central Adrenal Insufficiency.
Royal College of Paediatrics and Child Health (RCPCH)	Guideline	006	003	1.2.1 - Consider Adrenal Insufficiency in people with unexplained hyperpigmentation, or when there is no other clinical explanation for the presence of 1 or more of the following persistent symptoms, signs or features . In addition we add (primary or secondary amenorrhea, hirsutism, precocious puberty, infertility, acne and pubarche	Thank you for your comment. The committee considered your suggestions and agreed that early puberty should be added, but the other symptoms were thought to be too general or uncommon.
Royal Manchester Children's Hospital	Guideline	008	001	Table 1 - "8-9 am cortisol below 150 nmol/L – start management for Adrenal Insufficiency". We are concerned that following this recommendation may cause an over diagnosis of Adrenal Insufficiency in CYP and therefore a proportion of CYP will be started on glucocorticoids unnecessarily. 8-9 am cortisol levels below 150 nmol/L are within the normal range in some assays. (i.e 6am - 10 am cortisol reference range at RMCH is 133-537 nmol/L – Roche Gen II assay) It is not uncommon for CYP to present with one or more of the symptoms included in section 1.2.1 (nausea,	Thank you for your comment. A separate column has been made for children and young people under 16 years that states if cortisol is below 150 nmol/L the patient should be referred to paediatric services.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				vomiting, poor appetite, diarrhoea, or dizziness). For CYP with one or more of these non-specific symptoms, we do not think it is appropriate to start treatment for Adrenal Insufficiency on the basis of a 8-9 cortisol below 150 nmol/L. These symptoms are not uncommon in children and an 8-9 am cortisol level below 150 nmol/L can be normal depending on the assay. We suggest that these patients are referred or discussed with paediatric endocrinology before starting treatment for Adrenal Insufficiency.	
Royal Manchester Children's Hospital	Guideline	008	003	Neonates and young infants do not have circadian rhythm, therefore random cortisol can be performed as a baseline initial investigation in suspected cases of Adrenal Insufficiency. Also, a cortisol taken at any time of the day on a patient who is acutely unwell (with a suspected undiagnosed adrenal crisis) can be very helpful and diagnostic before starting hydrocortisone treatment.	Thank you for your comment. The committee has made a recommendation that cortisol can be measured at any time of day for people under the age of 1 and this should be interpreted by a specialist. The committee does not agree with measuring cortisol at any time in people over this age is of benefit because between 8-9am is the optimal time for peak cortisol levels.
Royal Manchester Children's Hospital	Guideline	026	015	"Decision to taper doses of glucocorticoids should be made by the clinical team who initiated the treatment". We agree with this statement. However, non-paediatric endocrine teams may not be able to work out what the daily physiological equivalent glucocorticoid dose is (when tapering down glucocorticoid treatment) – is it worth adding links to BNFc body surface area in children and a glucocorticoid conversion calculator?	Thank you for your comment. It would be usual for withdrawal of glucocorticoids in children to be done with advice from paediatric specialists. We would not typically replicate information provided in the BNF.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Sheffield Teaching Hospitals NHS Foundation Trust	Evidence Review C	General 012	General 015	If the committee wishes from our paper Debono et al NEJM Evidence 2023 2 (2) where we had 139 subjects assessed for steroid induced Adrenal Insufficiency and all had a waking fasting salivary cortisone and SST, we can analyse the waking saliva cortisone and cortisol and 9am serum cortisol cut-offs associated with confirmation or exclusion of AI in patients on steroids. We did carry out this analysis for serum cortisol for the "glucocorticoid induced AI guidelines" being designed by Endo society/ESE who contacted us. This will allow more consistency in cut-offs mentioned in the different sections in the NICE guidelines. The study referenced in the guidelines is from a study of 47 patients and the recommended cut-offs for saliva testing are for samples taken between 9am and 1030am. For an individual over 90 minutes cortisol levels can vary significantly and therefore the quoted cut-offs can result in significant numbers of false positives with many unnecessary referrals. A baseline salivary cortisone of 37.2nmol/l is equivalent to serum cortisol around 450 to 500nmol/l. These levels are way above the 300nmol/l cut-off being suggested to exclude AI.	Thank you for your suggestion. Unfortunately, we are unable to include this analysis at this stage of the guideline, but should it be published, it will be considered in any future updates of the guideline. For clarification, Evidence reviews C and D are overlapping. The population in C (people withdrawing from corticosteroids) is a subpopulation of those in D. The committee discussed the thresholds and the certainty in the evidence from the included paper in review C. They agreed that it wasn't enough evidence to base a recommendation on and agreed that the cut offs for 9 am cortisol tests should be the same as those used to screen for adrenal insufficiency in a general population. A cross reference was made to the committee discussion and recommendations in review D which included all people with suspected adrenal insufficiency including those who are withdrawing from glucocorticoids. Review D had included the Debono paper. Following consultation comments and further discussions, the committee amended the recommendations on thresholds, so they are now consistent across the different sections of the guideline.
Sheffield Teaching Hospitals NHS Foundation Trust	Evidence Review D	006	003	Is it possible to change "non-specialist" to "non-endocrine specialist"? I understand this is what is meant by reading the information about the "Population" in	Thank you for your suggestion. We are unable to change the wording of the clinical question at this stage

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Table 1. The information is directed to all specialists that are non-endocrine, GPs and other non endocrine healthcare workers.	but have changed "non-specialist" to "non-endocrine specialist" in the introduction to make it clearer.
Sheffield Teaching Hospitals NHS Foundation Trust	Evidence Review D	006	Table 1	I would add salivary cortisone here as this will always be the preferred saliva test for Adrenal Insufficiency when compared to saliva cortisol.	Thank you for your comment. The table is a summary of the review protocol which we are unable to change at this stage of the guideline. However, we were aware of the sparsity of the evidence in the area. Therefore, we did consider other tests such as salivary cortisone and included one paper (De Bono 2023) on salivary cortisone.
Sheffield Teaching Hospitals NHS Foundation Trust	Evidence Review D	010	Table 2	typo in Age for Debono et al	Thank you for your comment. This has been corrected.
Sheffield Teaching Hospitals NHS Foundation Trust	Evidence Review D	030	Table 11	Best say "fasting or waking salivary cortisol or salivary cortisone	Thank you for your comment. The table is a summary of the review protocol which we are unable to change at this stage of the guideline. However, we were aware of the sparsity of the evidence in the area. Therefore, we did consider these tests when searching for evidence.
Sheffield Teaching Hospitals NHS Foundation Trust	Evidence Review D	031	022	May the line "No relevant diagnostic test accuracy studies of salivary cortisone were identified" be more specific to what it is referring to please? Is this for paediatric studies or for any age group. If it's the latter, then Debono et al (ref 5) is a diagnostic accuracy study testing salivary cortisone.	Thank you for your comment. The text "No relevant diagnostic test accuracy studies of salivary cortisone were identified" has been deleted as we had indeed included the Debono study on salivary cortisone.
Sheffield Teaching Hospitals NHS Foundation Trust	Evidence Review D	045	030	Agree to say one can try switching to a transdermal preparation for HRT but do we have strong evidence to say cortisol result is not affected? Should one add a	Thank you for your comment. There is currently no strong evidence to suggest cortisol results are not affected by switching to transdermal preparations and

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				reference here? More studies are needed in this area. Instead of suggesting stopping OCP for 6 weeks can one explicitly ask for the use of salivary cortisol measurements in these patients (El-Ferhan et al JCEM 2024 vol 109 579).	we agree that more studies are needed in this area. In the meantime, the committee used their clinical expertise and consensus to make a recommendation in this area. The committee has recommended that if for example, an adrenal crisis is suspected in a person taking oral oestrogens cortisol can be measured but the use of oral oestrogens need to be taken into account when interpreting serum cortisol results.
Sheffield Teaching Hospitals NHS Foundation Trust	Evidence Review D	045	046 – 048	It is mentioned that a patient with a serum cortisol 200nmol/l – 300nmol/l should be referred for SST if repeat morning cortisol remains in this grey zone. At the beginning of the paragraph, on the other hand I agree when it is commented that the clinical context should be taken into consideration. Most of the testing for Adrenal Insufficiency is mainly to look for steroid induced adrenal suppression. A cortisol level between 200 to 300nmol/l in a patient on steroids might not be followed up with a SST but a clinical decision for weaning or repeating after a few months or just sick day education so may be one should be more specific in the sentence on lines 46 – 48 on who should be referred for SST. Maybe one can here add reference to the section “”Evidence review C: When to refer for specialist investigation when withdrawing corticosteroids” for patients being withdrawn off steroids so that an endocrinologist decides whether SST is	Thank you for your comment. We agree this is a grey area and needs consideration if the Synacthen test is of value. The committee have reviewed and amended the recommendations to serum cortisol test results between 150-300 nmol/L to consider repeating the test and if the level remains the same seek advice from endocrinology services. Advice can then be given as the best course of action including if Synacthen is needed.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				needed and not all get a SST (Evidence review C lines 30-32 pg 13). The main draft is more clear on this point (page 8 1.2.9)	
Sheffield Teaching Hospitals NHS Foundation Trust	Evidence Review D	046	008	I would add as other reason to carry out research on the use of saliva is to learn the "implementation process" when initiating the use of saliva in an institute.	Thank you for your suggestion. The Committee can only make research recommendations on areas where they have conducted a systematic review and identified evidence gaps that could be addressed with new research. The systematic review for Evidence Review D focused on initial investigations' and therefore the committee could not make recommendations on 'implementation processes'.
Sheffield Teaching Hospitals NHS Foundation Trust	Evidence Review D	047	002	Some patients e.g shift workers, late sleepers might have a very low cortisol on waking. Would one consider changing the line to saying that unless there is an obvious reason for a low morning cortisol <150nmol/l e.g shift worker and can be tested urgently then one would start treatment until formal testing is carried out?	Thank you for your comment. We have added the following clarification to the Committee discussion of the evidence review D: The committee also wished to highlight that shift workers may have variation in diurnal rhythm, and this should be taken into consideration when interpreting the results.
Sheffield Teaching Hospitals NHS Foundation Trust	Evidence Review D	156		Typo in current evidence base which should say salivary cortisol and cortisone.	Thank you for your comment. This has been corrected.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Sheffield Teaching Hospitals NHS Foundation Trust	Evidence Review E	General	General	When discussing corticosteroid withdrawal, one could consider recommending following steroid sick day rules for a period after patients have been completely withdrawn. Some studies indicate higher mortality in the period after steroid cessation e.g Mebrahtu et al JCEM DOI: 10.1210/jc.2019-00153, Einarsdottir Endocrine Connections (2024) 13 e230535 https://doi.org/10.1530/EC-23-0535.	Thank you for your comment. This is covered in the following recommendation in section 1.9 of the guideline: Tell people who are tapering glucocorticoid doses below a physiological equivalent dose: • to expect temporary symptoms, including fatigue, reduction in appetite and low mood • about sick-day rules and glucocorticoid cover for invasive procedures and surgery
Sheffield Teaching Hospitals NHS Foundation Trust	Evidence Review E	019	004	In the guidelines it is commented that patients do not have to be converted from prednisolone to hydrocortisone. Admittedly we do not have any prospective studies to support this, but we are aware that many physicians do make this change. One could consider reviewing the study Arshad et al JCEM 2024 doi.org/10.1210/clinem/dgae059 which describes the outcome of patients after they have been weaned down to physiological prednisolone dose (the studies reviewed for the Corticosteroid withdrawal document, as commented on page 18 line 15, did not give enough detail on how to taper once on physiological dose). It does give adrenal-insufficiency outcomes and indicates how patients are monitored. The study does compare patients converted to hydrocortisone as a comparator group but is retrospective so data will NOT be of high quality. Similarly, Sagar et al Clin Endocrinol (Oxf) 2021	Thank you for your comment. The review stated that a search for non-randomised studies would only be conducted 'If insufficient RCT evidence is available for the committee to make recommendations'. Having included 6 RCTs and drawing on their clinical expertise, the committee was able to make recommendations and did not review any non-randomised studies. In addition, both Arshad and Sagar did not include any multivariate analyses which was a prerequisite for any non-randomised study to be included and therefore would not have fulfilled the criteria in our protocol.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Mar;94(3):361-370. doi: 10.1111/cen.14405 retrospectively compares prednisolone to hydrocortisone weaning.	
Sheffield Teaching Hospitals NHS Foundation Trust	Guideline	021	011	1.7.5 - Why have no doses been suggested for hydrocortisone infusion pumps and im/iv hydrocortisone injections during adrenal crisis? They could be helpful for the non endocrine specialists working in ED for instance. Maybe a reference could be used on this line?	Thank you. Where the dosages are the same as those in the BNF they have not been replicated within the guideline recommendations. The reader should refer to the BNF for further information.
Sheffield Teaching Hospitals NHS Foundation Trust	Question	1		The draft recommendations are straightforward and target the health care workers who will largely be using these guidelines.	Thank you for your comment. The committee is pleased that you found the recommendations straightforward.
Sheffield Teaching Hospitals NHS Foundation Trust	Question	2		No as most of the recommendations are already being followed in our centre.	Thank you for your response.
Sheffield Teaching Hospitals NHS Foundation Trust	Question	3		I agree with the cut-offs being suggested.	Thank you for your response.
Sheffield Teaching Hospitals NHS Foundation Trust	Question	4		I agree with the doses being suggested.	Thank you for your response.
Sheffield Teaching Hospitals NHS Foundation Trust	Question	5		Fine this is acceptable, and the references are of excellent quality	Thank you for your response.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Sheffield Teaching Hospitals NHS Foundation Trust	Question	6		Yes I do agree with tapering regimes although more studies are needed in this area. Tapering down prednisolone by 1mg every 4 weeks during the slow wean when on physiological dose is also reasonable as an alternative. With regards to the decision to measure a morning cortisol only when the slow tapering fails, and the patient shows symptoms/signs of Adrenal Insufficiency I feel might increase risk of weaning patients off who still have adrenal suppression. A morning cortisol is quite straightforward to measure and most of these patients are in secondary care. Having a normal cortisol can also give confidence to wean rapidly, suggests whether a patient needs to continue following sick day rules once off the steroids and for how long. Some patients may be asymptomatic although cortisol levels are borderline low but then cannot respond to stress. In the meta analysis by Broersen et al 88/98 patients with Adrenal Insufficiency did not report symptoms (J Clin Endocrinol Metab, June 2015, 100(6):2171–2180).	Thank you for your response. The committee discussed the lack of evidence in this area and have made a research recommendation.
Sheffield Teaching Hospitals NHS Foundation Trust	Research Advice			1. Oe could suggest further research in paediatric patients and diagnostic studies for AI. Other studies are needed to investigate testing for AI in patients on OCP, HRT, transdermal or oral. For salivary cortisone we have carried out a diagnostic accuracy study but it is understandable to request more similar studies. Testing of cut-offs could be carried out in	Thank you for your suggestion. The committee focused the research recommendations on priority areas and decided that salivary cortisol would have the largest impact on future recommendations.

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				longitudinal studies, assessing cost effectiveness, taking into consideration any hospital admissions, adrenal crises, use of sick day rules, QOL.	
Sheffield Teaching Hospitals NHS Foundation Trust	Research Advice			Prospective study comparing patients weaned off completely using prednisolone compared to patients converted to hydrocortisone – outcome: time to successful wean with reactivation of adrenal axis.	Thank you for your suggestion. The committee focused the research recommendations on priority areas and decided further research was needed for people on prednisolone for immune or inflammatory conditions because there is uncertainty on how to manage them optimally when it comes to withdrawing treatment.
Society for Endocrinology	Guideline	008	001	table on random cortisol. Doesn't comment on type of assay. Important for ref ranges I think.	Thank you for your comment. The reference ranges will depend on the type of assays used. Test results should be interpreted based on established local assays and corresponding cut-offs. The following clarification can be found in the Rationale and Impact section and the 'committee's discussion of the evidence' section in Evidence review D: *The committee discussed the difficulties in setting cut-off points, as these vary greatly depending on the assay used and only have clinical use if specific to a particular assay. However, the committee agreed that it would be useful for non-specialists to have some guidance on at what point to refer onwards (providing it is highlighted that the cut-offs are only for use with modern*

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					immunoassay assays and that local guidelines may need to be followed if alternative assays are used).
Society for Endocrinology	Guideline	015	006	1.4.7 *Think about seeking endocrinology specialist advice if needed.*I think if anyone is on iv hydrocortison or regular im hydrocortisone they should have endocrine advice, not think about it.	Thank you for your comment. This has been changed to seek endocrinology specialist advice.
Society for Endocrinology	Guideline	016	003	*1.4.11* *11 Offer blue steroid treatment cards to people on exogenous glucocorticoids 4 for non-endocrine conditions who are at risk of tertiary adrenal 5 insufficiency.* I assume there is still politics around blue steroid cards. To me it is confusing to have the red and blue steroid cards.	Thank you for your comment. Currently the two cards have different purposes and healthcare professionals are aware of their different uses. The merging of red and blue cards is currently under discussion with the NHS Chief Medical Officer, but this is not imminent, and the blue steroid cards are currently still in use.
Society for Endocrinology	Guideline	020	022	*1.7.1* *Give intravenous or intramuscular hydrocortisone for suspected adrenal 23 crisis without delay,* I appreciate the evidence is slight but imperative (in my opnion) to come up with reasonable time limit to what 'without delay' means, particularly given long waits for ambulances/A&E review/admitting. In the explanation it says 'immediately' and wonder if this could be specified particularly due to the considerable stress patients feel waiting for treatment in ED.	Thank you. The committee have revised the wording in the recommendation to immediately.
Society for Endocrinology	Guideline	021	011	*1.7.5*	Thank you for your comment. The recommendation has been amended to clarify that IV infusion should only be

Adrenal insufficiency: identification and management

Consultation on draft guideline - Stakeholder comments table
08/03/2024 – 19/04/2024

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				*Continue to give hydrocortisone by intravenous infusion over 24 hours, or 12 intramuscular or intravenous injections (4 times a day) until the person is 13 haemodynamically stable and they are able to take and absorb oral 14 glucocorticoids.*I am concerned about the recommendation for iv hydrocortisone without the qualification that this should be in a high dependency setting or a comment on securing iv access. A cannula tissuing over night could lead to a long delay and precipitating a crisis if on a general ward.	administered where the person can be monitored to ensure no interruption of the infusion.
Society for Endocrinology	Guideline	024	002	1.8.8 8 *consider measuring renin and adjust fludrocortisone dose if needed.* Weak comment to me without qualification about how to adjust (presumably alluding to doing so if suppressed).	Thank you for your comment. The committee chose to use 'consider' because while measuring renin may be beneficial to some patients, this doesn't need to be routinely screened if there are no symptoms indicating any issues with fludrocortisone dosing. Renin levels have not been shown to correlate with symptoms.

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*